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Original Communications

SEVENTEEN CASES OF LEFT INTRAVENTRICULAR BLOCK WITHOUT INCREASED HEART SIZE

A. F. NYSSENS, M.D., A. VAN BOGAERT, M.D., AND
A. VAN GENABEEK, M.D.

ANTWERP, BELGIUM

GENERALLY, and with reason, an increased duration of the QRS complex of the ventricular electrocardiogram beyond 0.08 second is considered to be due to delayed intraventricular conduction, provided the auriculoventricular conduction time is normal. The location of the damage corresponding to a special bundle branch block pattern is more often open to discussion, although the precordial leads generally allow the discrimination between right and left bundle branch block with apparent precision. The standard limb leads do not always do so, and the rare type of bundle branch block has been proved to be left in many instances, just as is the common type.

The right bundle branch block pattern, as described by Wilson, seems to be constantly due to a slowed conduction through the right branch of the bundle, and Bayley's variations of this type, even with left axis deviation of QRS, can be related to various positions of the heart in the same manner as the common type of left bundle branch block can be changed into the rare type by changing the heart position.

An increased heart size in itself has been suggested as one of the causes of a prolonged QRS duration (Rasmussen). This association, however, has some exceptions. All agree that a Wilson block often occurs in a heart of normal size (Wolferth and Wood, and others), and, perhaps for this reason, it can have a good prognosis (von Deesten and Dolganos). Left bundle branch block without increased heart size is considered to be a rare phenomenon by Master and associates, Lenègre and Chevalier, and Yater.

We have been interested in investigating the part played by increased heart size in the pathogenesis of the common type of bundle branch block. Seventeen observations of ambulatory patients showed a normal, or approximately normal,

From the Cardiological Department, Bunge Institute, Berchem-Antwerp, Belgium.
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heart volume on x-ray examination and a more or less typical left bundle branch block pattern in the standard leads. They have been examined by multiple precordial leads, and the diagnosis of left bundle branch block was verified in all. The block was always an electrocardiographic finding, suspected in some patients by the existence of auscultatory anomalies considered characteristic by certain authors, i.e., presystolic reduplication of the first heart sound and reduplication of the second sound.

The clinical diagnosis in our cases was variable. The blood pressure was never over 200 mm. Hg systolic and 100 mm. Hg diastolic. Seven had a blood pressure not over 150 mm. Hg systolic and 100 mm. Hg diastolic, seven had angina pectoris, two had acute pulmonary edema, and eight had various diffuse and subjective complaints. In all, the intraventricular block was permanent and did not change electrically.

TABLE I.

CASE NO.	SEX	AGE	DIAGNOSIS
1. Sl.	F	28	Neurocirculatory asthenia, irritable colon, Roger's disease; blood pressure 125/80
2. Sp.	F	55	Cardiospasm, paroxysmal auricular fibrillation, fainting spells; blood pressure 170/90
3. Ba.	F	48	Chronic malaria, varicose veins, neurosis; blood pressure 150/80
4. Ve.	F	52	Menopausal syndrome, fibrous lung tuberculosis, neurosis; blood pressure 190/90
5. Bo.	M	63	Chronic bronchitis, angina pectoris on exertion; blood pressure 200/90
6. Ve.	M	70	Mitral insufficiency, dyspnea on exertion; blood pressure 130/80
7. Co.	M	52	Angina pectoris, colitis; blood pressure 180/100
8. Bo.	M	54	Angina pectoris, chronic bronchitis; blood pressure 160/90.
9. V. d.B.	M	60	Obesity, cerebral and coronary circulatory insufficiency, myocardial degeneration; blood pressure 140/80
10. Ja.	M	62	Neurosis; blood pressure 180/90
11. Se.	M	58	Intermittent claudication, angina pectoris, dizziness (Stokes-Adams syndrome?); blood pressure 160/80
12. Ro.	M	46	Chronic bronchitis, angina pectoris; blood pressure 125/80
13. V. R.	F	57	Colitis, cholecystitis (?); blood pressure 190/100
14. Pu.	F	59	Neurosis, formerly hypertension; blood pressure 150/80
15. Ko.	M	48	Anxiety, gastric ulcer, obliterating endarteritis, angina pectoris; blood pressure 170/100
16. Ki.	M	66	Pulmonary edema, angina pectoris (1940, infarction with left bundle branch block), extracardial tumor beside apex; blood pressure 150/85
17. D. V.	M	61	Pulmonary embolism, endarteritis obliterans, hemianopsia and dysarthria, mitral insufficiency; blood pressure 150/90

The following x-ray prints show a normal, or approximately normal, heart volume. In their respective electrocardiograms several tracings show a normal QRS axis in the standard leads and/or a positive or diphasic T wave in Leads I and V_5.

The QRS duration varied from 0.12 to 0.15 second. The precordial leads of the electrocardiogram showed a delay of the intrinsicoid deflection over the left precordium varying from 0.08 to 0.11 second (respectively, 9, 10, 11, 9, 10, 11, 9, 11, 9, 8 hundredths of a second). No tracing showed a Q wave in Lead I or over the left precordium.

Four patients had a normal electrical axis (concordant type of bundle branch block), three of whom had a positive T wave in Lead I and the fourth a diphasic T_1 of the minus-plus type. In seven other tracings with left axis deviation T_1 was positive. In the 8 tracings shown T in V_5 is positive five times for four positive T waves in Lead I and one diphasic T_1 of the minus-plus type.

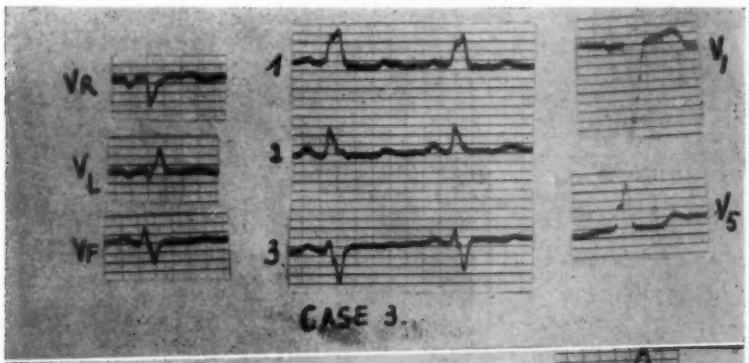


Fig. 1.

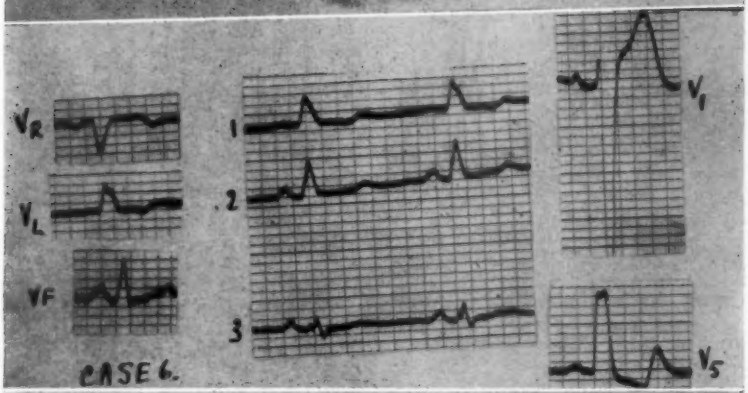


Fig. 2.

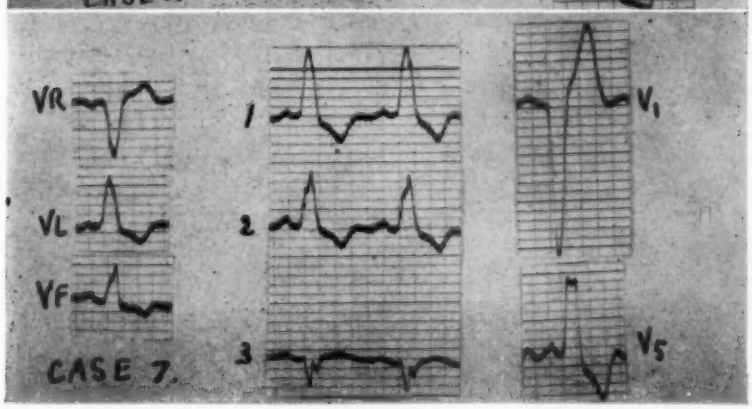


Fig. 3.

There was not always definite evidence of heart disease in our patients. Atypical patterns in the peripheral leads such as a positive T wave in Lead I (and V_5) seem to be directly related to the absence of myocardial hypertrophy and in a lesser degree to heart position. Variation in heart position has its most

striking effect upon the peripheral leads. This is so for QRS and also for the T wave, of which we could observe some respiratory electrical axis variations.

DISCUSSION

The anatomy of the His bundle and its pathological anatomy help to explain a complete left bundle branch block tracing with a heart of normal size.

Fig. 4.

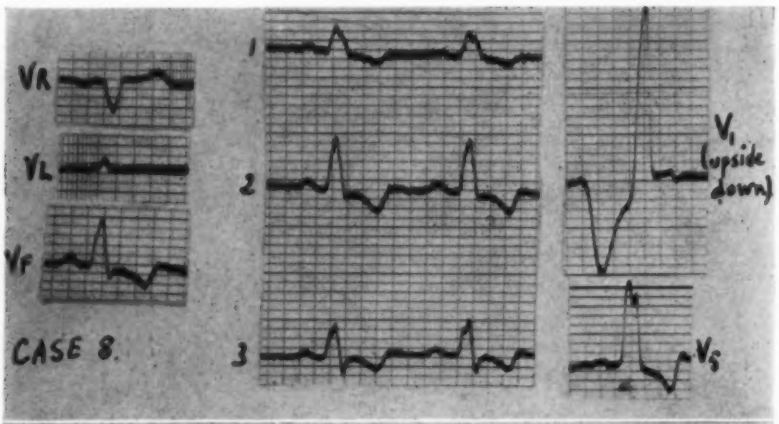


Fig. 5.

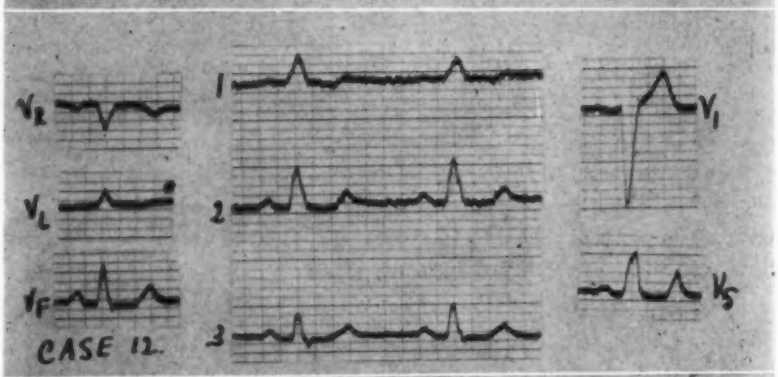
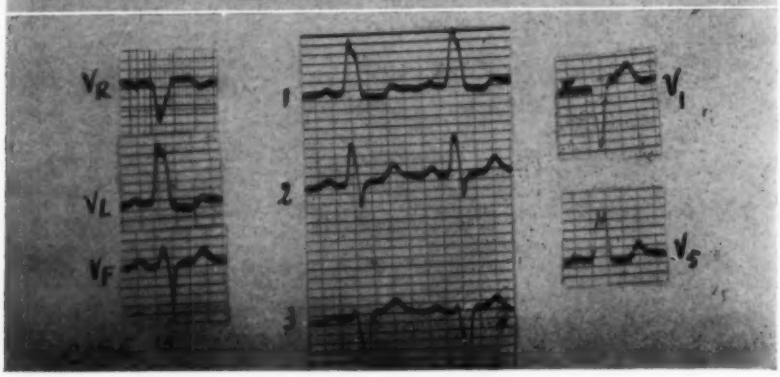


Fig. 6.



According to Mahaim's studies, the His bundle measures only a few millimeters from its origin in the Tawara node. Very shortly it gives off its left roots, which all together are called the left branch.

The right branch is the prolongation of the His bundle and continues to the lower part of the interventricular septum without giving off any subdivisions. In certain cases, there are very high auriculoventricular connections, sometimes from the Tawara node itself.

The arterial blood supply of the left branch is mixed and comes principally from the anterior interventricular artery, while the posterior ramifications, fed by the posterior interventricular artery, are fewer in number. In ten per cent of the cases, the posterior perforating arteries proceed from the left coronary artery, when the latter, through the circumflex artery, gives off the posterior interventricular artery.

Fig. 7.

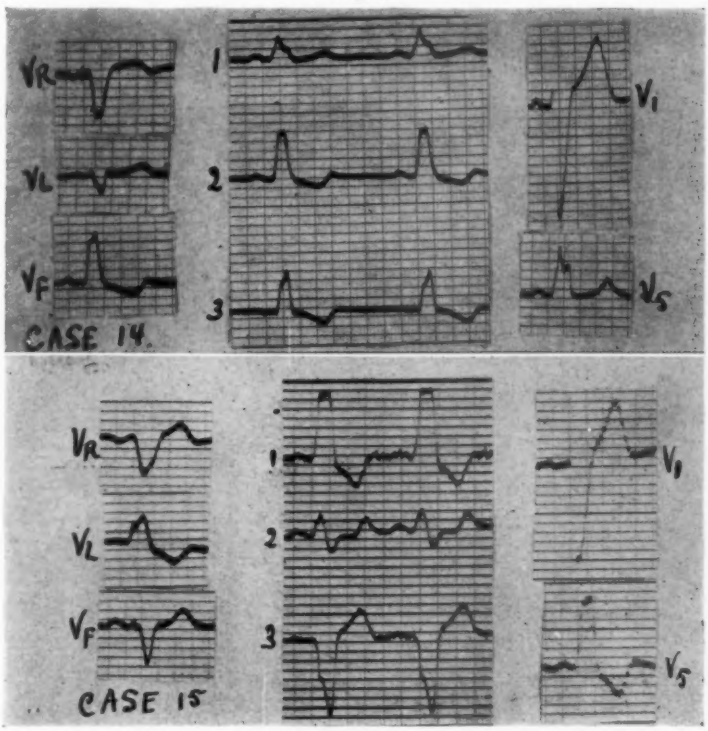


Fig. 8.

The right branch is exclusively irrigated by the anterior perforating arteries, and so by the left coronary artery. The middle and lower parts of the right branch may be nourished by an individual artery, the ramus limbi dextri (Gross), issuing from the second anterior perforating artery. Gross stated that the lower portion of the right branch is supplied by this ramus limbi dextri and moreover by some anastomotic branches between this ramus and the right coronary artery by way of a few arterioles in the vicinity of the anterior pillar of the right ventricle. Some other anastomotic branches exist in the septum between the right and left coronary network (Laubry, Soulié, and Thys).

The pathological causes which may influence the conduction of the entire left branch can be anatomical or functional and must be located in the uppermost part of the septum.

Cardiac traumatism can be the cause of septal injury and resulting bundle branch block even in the absence of a perforating wound, but this did not occur in any of our patients.

Congenital malformation plays only a small role in the pathogenesis of intraventricular block. Indeed, embryologically (Mahaim) the His bundle develops very early, is well formed in the fifth week of intrauterine life, and is almost always present even in septal malformations, including the cor triloculare biatriatum and the cor biloculare where it is situated in the posterior part of the ventricle. It is absent only when the septum inferius is not formed.

Localized endocardial lesions, such as septal endocarditis, are more frequent, causing an endocardial block of the left bundle branch, as reported by Mahaim and by Jouve, Senez, and Pierron. The hypothesis of fetal endocarditis or other malformation is striking in one of our cases.

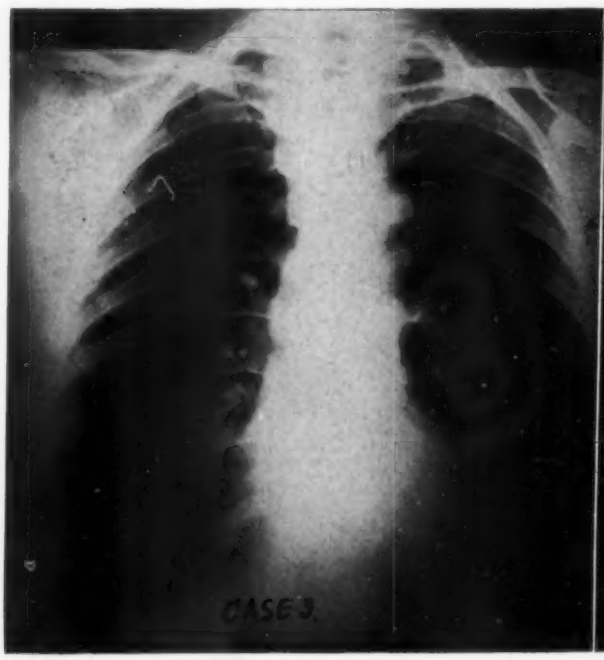


Fig. 9.

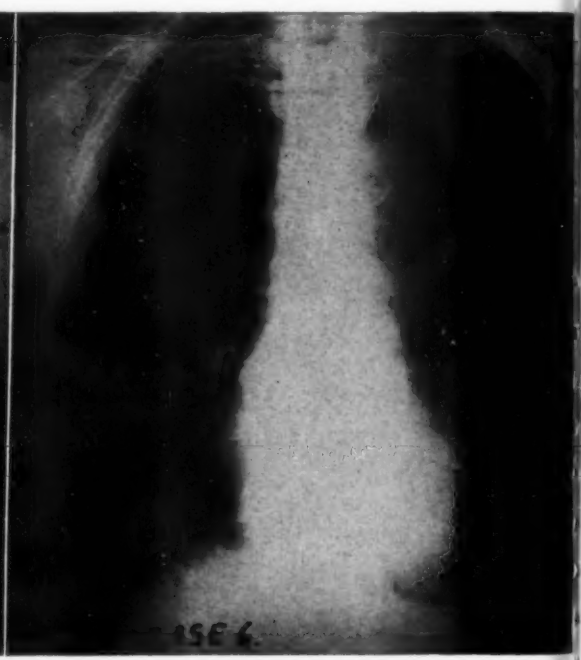


Fig. 10.

Localized vascular damage, and principally septal infarction, is the most frequent cause of left bundle branch block (Soulié and Laham). The infarction in this case must be purely septal and high. Indeed, peripheral block cannot be excluded if the infarct lies on the lower septum or in the free ventricular wall. The block then can originate in the Purkinje-myocardial synapses and thus be focal (away from the bundle branches).

Several anatomical studies have been made in an attempt to find a correlation between the location of bundle branch block and the obliterated artery in the presence of an infarction (White, Lenègre and Chevalier, and Somerville and Wood), but they could not establish a definite relationship. In 80 per cent of infarctions with bundle branch block, there is a septal lesion.

On the other hand, there is not necessarily bundle branch block in cases of septal infarction (Mahaim: Anastomoses), and right bundle branch block just as left is frequently observed in both anterior and posterior infarction (Somerville and Wood).

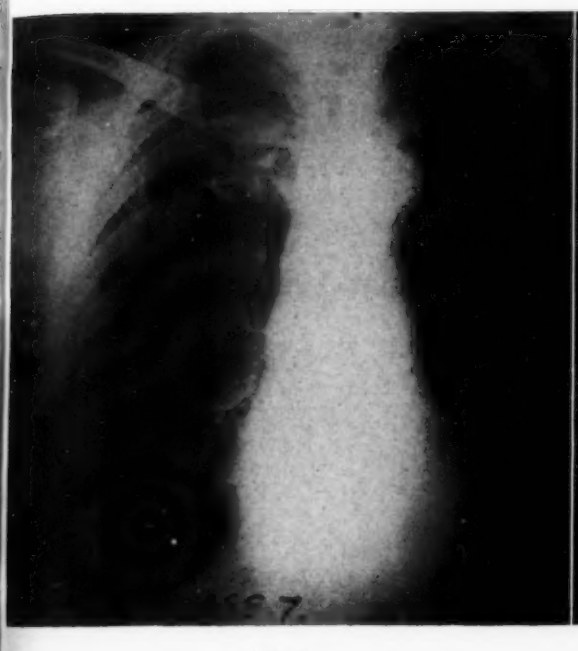


Fig. 11.

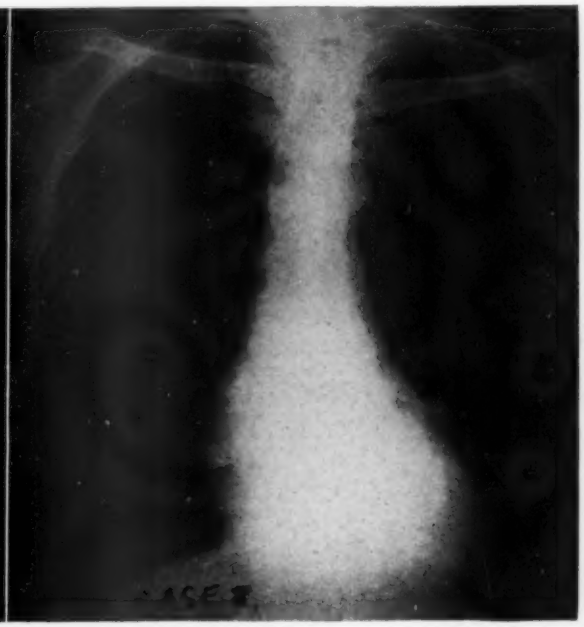


Fig. 12.

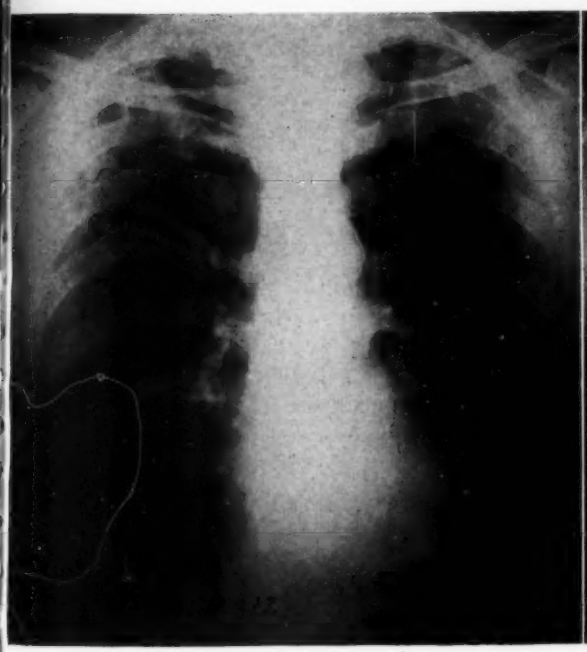


Fig. 13.

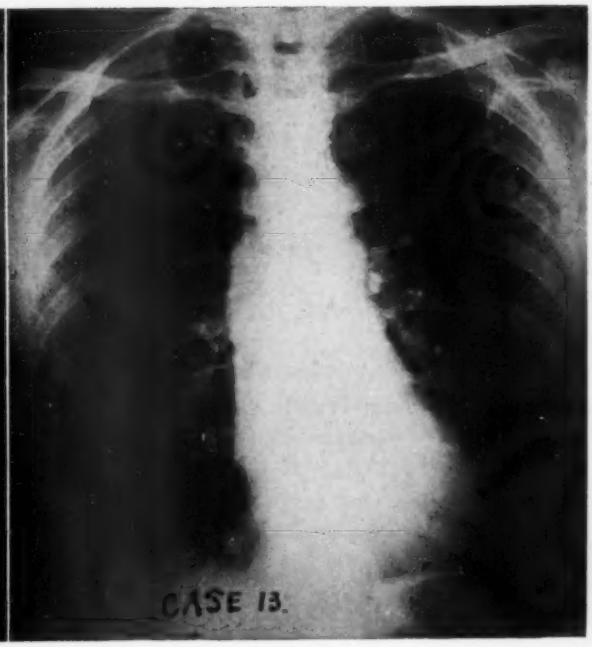


Fig. 14.

Functional or mixed functional plus anatomical lesions exist in many instances of bundle branch block, as noted in the literature (Yater). An example is encountered in 20 per cent of infarctions with bundle branch block in which there is no septal participation, and another exception exists in the occasional regression of the bundle branch block pattern after thoracolumbar sympathectomy for arterial hypertension with bundle branch block, even in the presence of a big heart (then mixed with peripheral lesions). Our own cases without objective findings also illustrate this event.

The classical distinction between complete (or major) and incomplete (or minor) bundle branch block seems to be of real value, at least for left bundle branch block. All our patients had a left bundle branch block pattern with a QRS duration of 0.12 second or more. If this distinction in relation to the QRS duration is correct, the difference between complete and incomplete left bundle branch block becomes a matter of degree and location of the impairment

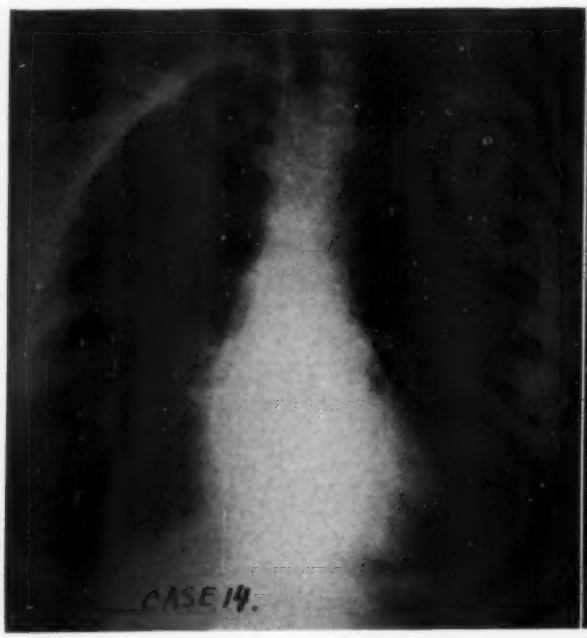


Fig. 15.

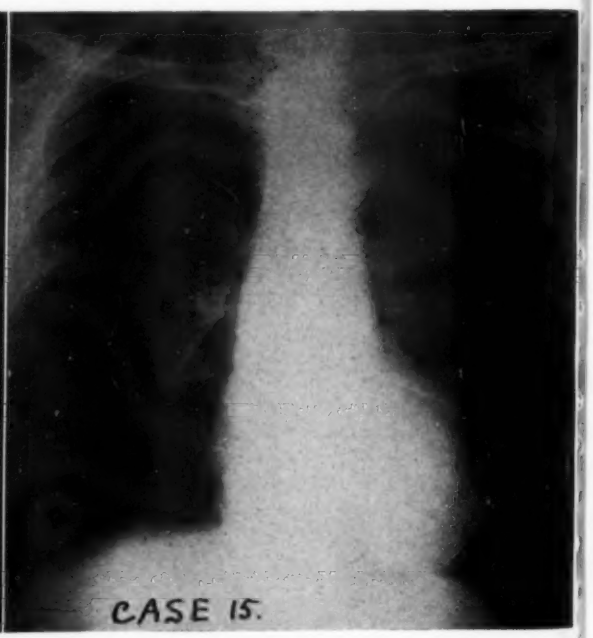


Fig. 16.

of the left conduction pathways. Such an impairment can have a functional or anatomical origin. It is caused in some instances by an anatomical destruction of the entire left branch, as recently reported by Lenègre and Chevalier, and then corresponds to a complete left bundle branch block pattern. Whether or not the heart has an increased size depends only on the presence or absence of additional peripheral myocardial damage. The higher the location of the bundle branch disturbance, the more likely will the left block be complete.

It is hazardous to give a prognostic significance to bundle branch block. The prognosis does not depend on the type of block, but rather on the causal disease and its extension. The block can be intermittent or disappear com-

pletely after a while. We insist upon the good prognosis of a whole series of our patients, eight of whom have no definite evidence of heart disease; nevertheless, their block is constant in appearance and invariable over a period of several years.

Not only an anatomical destruction, but any change in chronaxy of the His bundle and its branches or of a segment of it, can produce a broadening of the QRS complex (van Bogaert). Moreover, a left bundle branch block pattern often corresponds to bilateral or exclusively right branch lesions (Lenègre and associates), and important and diffuse lesions of one or both branches, sometimes with complete interruption, do not always correspond to a bundle branch block tracing of the electrocardiogram.

The appearance of a bundle branch block pattern after an auricular extrasystole (Segers) or on effort (Wilson and associates[18]) may be an argument for its functional origin. An altered chronaxy of the conduction pathways may be of auricular origin.

A defective transmission through the Purkinje-myocardial synapses is suggested by Segers, and this hypothesis corresponds to the one proved by one of us in 1933, i.e., that simple changes of the respective myocardial and His-bundle chronaxies alter the QRS duration. Almost with certainty such a defective transmission implicates a serious damage of the myocardium and *ipso facto* an increased ventricular volume when the transmission defect depends upon the receptivity of the myocardial tissue. Yet, in none of his experiments, could van Bogaert obtain an exclusive alteration of the myocardial chronaxy which was important enough to increase the duration of QRS.

An altered bundle branch chronaxy was capable of altering the duration of the intraventricular conduction. Of course, such an alteration, highly located and at the left of the His bundle, can not implicate a change in heart volume. This last hypothesis of functional trouble, or of an anatomical lesion of the same region, must be advocated, we think, in a case of left bundle branch block with a heart of normal volume.

CONCLUSIONS

A left bundle branch block pattern in a heart of normal size is not a rare phenomenon. Our seventeen cases of this finding showed a complete left block. This is an argument for its high septal origin, between the Tawara node and the left ramifications. The normal heart volume is another point supporting high and localized septal damage, since a bundle branch block pattern can be caused by pure peripheral or mixed peripheral and septal damage. In such cases an increased heart size can be expected. A surprisingly important percentage of atypical standard leads is found.

The T wave in Lead I was positive in ten patients out of seventeen. This may be due in part to the absence of a hypertrophy curve which should deform the pure bundle branch block tracing. The electrical axis of QRS was normal in about 25 per cent of the cases (four out of seventeen), and never was there a Q wave in Lead I or over the left precordium. This normal QRS axis can be related to the absence of a hypertrophy curve complicating the bundle branch block, but also to the relatively vertical position of the heart. Left axis deviation is not directly related to left bundle branch block.

We wish to express our gratitude to Dr. P. D. White who kindly edited the text.

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THE ELECTROCARDIOGRAM IN PREGNANCY AND THE PUERPERIUM

JACOB ZATUCHNI, A.B., M.D., M.S. (MED.)*

PHILADELPHIA, PA.

OBSERVATIONS of the electrocardiographic changes in normal pregnancy have been based on bipolar leads in which the distant electrode has significant voltage and varies not only from individual to individual, but also in the same individual from time to time. Wilson and associates[21] suggested a method for the electrocardiographic study of the human heart employing indirect leads which record the potential difference between an exploring electrode and one remaining at or near zero voltage. Such leads closely resemble direct leads from the ventricular surface.[5]

This electrocardiographic study, employing unipolar leads, is concerned particularly with late pregnancy and the early puerperium, for a change occurring in either period would be more apparent in relation to values obtained in the other. Its purposes are: first, to define the positional changes in terms of the mean electrical axis of QRS and the electrocardiographic position, and, second, to determine whether there is any evidence of ventricular hypertrophy.

SUBJECTS AND METHODS

Twenty-five normal patients, each with uncomplicated pregnancy, delivery, and post-partum course, were studied. Eleven were white and 14 Negro. The ages varied from 16 to 40 years. The weight at term varied from 116¼ to 118 pounds, the average gain in weight being 20 pounds.

Electrocardiograms were obtained ante partum, within 24 hours after delivery, and during the early puerperium. The term "ante partum" when used for purposes of comparison includes only the final tracing taken before delivery. This was obtained within 30 days of delivery in 24 patients. The interval varied from 2 hours to 50 days, the average being 14 days. The term "day of delivery" when used for purposes of comparison includes those tracings taken within 24 hours after delivery. The interval varied from 1 hour to 22.5 hours, the average being 11.3 hours. The term "post partum" when used for purposes of comparison includes those tracings taken 2 to 5 days after the day of delivery. A total of 98 electrocardiograms was obtained.

RESULTS

Electrocardiographic Position of the Heart. — Of 5 patients with initial electrocardiograms 100 to 155 days before delivery, the position changed with ad-

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*Instructor in Medicine, Temple University School of Medicine and Hospital, Philadelphia.

vancing pregnancy in 3, the change being from the semivertical to the intermediate in 2 and from the vertical to the semivertical in 1. Of 4 patients with initial electrocardiograms 82 to 92 days before delivery, the position changed in 2, 1 from the vertical to the semivertical, the other from the semivertical to the intermediate to the semivertical. Thus, of 9 patients with initial electrocardiograms 82 to 155 days before delivery, 4 showed no change in the electrocardiographic position of the heart with advancing pregnancy.

Comparing the tracings taken on the day of delivery and post partum with those taken ante partum, no change in position was observed in 18. Furthermore, the post-partum tracings, in comparison to those on the day of delivery, revealed no change in position in 21.

The electrocardiographic position of the heart in the various periods of observation may be found in Table I.

TABLE I. THE ELECTROCARDIOGRAPHIC POSITION AND THE DIRECTION OF THE MEAN ELECTRICAL AXIS OF QRS

ANTE PARTUM		DAY OF DELIVERY		POST PARTUM	
POSITION	AXIS (DEGREES)	POSITION	AXIS (DEGREES)	POSITION	AXIS (DEGREES)
IM	32.0	SV	38.0	IM	34.0
SV	60.0	V	85.0	V	59.0
SH	14.0	SH	17.0	SH	5.0
IM	24.0	SV	40.0	ID	34.0
SH	45.0	SH	47.0	SH	46.0
SV	32.0	SV	44.0	SV	36.5
SV	34.0	SV	49.0	IM	46.5
IM	12.5	SH	22.0	IM	32.5
SH	8.0	H	16.5	H	13.0
V	84.5	V	95.0	V	96.0
IM	42.0	IM	44.0	IM	42.0
SV	67.0	SV	68.0	SV	66.0
IM	26.0	ID	32.5	SV	40.0
SV	51.0	SV	78.0	SV	74.0
IM	20.0	IM	37.0	IM	26.0
IM	30.0	IM	43.0	IM	34.0
ID	46.5	V	76.0	SV	62.0
SV	65.5	V	78.5	V	77.0
V	144.5	V	86.0	V	95.0
IM	17.5	IM	19.0	IM	18.0
SV	52.3	SV	59.0	SV	64.0
SV	57.5	SV	63.0	SV	64.0
SV	45.0	SV	48.0	SV	47.5
V	66.5	V	72.0	V	77.5
SV	42.0	SV	46.5	SV	40.0

V = vertical H = horizontal IM = intermediate
SV = semivertical SH = semihorizontal ID = indeterminate

The Mean Electrical Axis of QRS.—Of 5 patients with initial electrocardiograms 100 to 155 days before delivery, 4 showed a shift of the axis to the left with advancing pregnancy. During the last month of pregnancy, it shifted back to the right in 3 of these 4 patients. In the fifth patient, the axis first shifted slightly to the right and then with advancing pregnancy to the left again.

Three of 4 patients with initial electrocardiograms 82 to 99 days before delivery showed a shift of the axis to the left with advancing pregnancy. In one of these, the axis shifted to the right again before delivery.

In the latter part of pregnancy, the direction of the axis varied from 8 degrees to 144.5 degrees, the average being 44.8 degrees. On the day of delivery, the axis shifted to the right in 24 subjects, varying from 1 degree to 29.5 degrees and averaging 10.1 degrees. Post partum, the axis shifted to the right in 19, varying from 0.5 degrees to 23 degrees and averaging 9.1 degrees (Table I).

The R Wave in the Precordial Leads.—In V_1 the R wave was present in all tracings but 3, in each of which a QS deflection was present. To the left of this, the R wave usually progressively increased in amplitude to a maximum value and then slightly decreased. The maximum voltage was usually recorded in V_4 or V_5. In no instance was it greater than 26.0 mv. A summary of the R-wave measurements may be found in Table II.

TABLE II. THE R WAVE IN THE PRECORDIAL LEADS (IN MILLIMETERS)

LEAD	ANTE PARTUM			DAY OF DELIVERY			POST PARTUM		
	AVERAGE	MINIMUM	MAXIMUM	AVERAGE	MINIMUM	MAXIMUM	AVERAGE	MINIMUM	MAXIMUM
V_1	2.2	0.0	4.8	2.1	0.0	4.5	2.2	0.0	5.0
V_2	5.8	0.2	10.0	5.5	0.2	11.0	5.3	0.5	10.4
V_3	7.7	0.8	20.2	7.3	1.3	20.0	6.8	1.3	15.0
V_4	11.2	1.8	22.0	12.8	6.5	21.0	12.3	4.2	22.0
V_5	11.0	6.1	18.0	13.4	7.0	26.0	12.2	6.8	18.0
V_6	9.6	4.0	14.8	10.2	5.0	19.0	9.6	5.0	15.0

The R/S Ratio in the Precordial Leads.—The smallest R/S ratio was usually in V_1 and the greatest in V_5 or V_6. The precordial lead in which the ratio first equalled 1 or more was usually V_3 or V_4, rarely V_2 or V_5. On the day of delivery, this zone of transition remained at the same lead in 13 instances, whereas in 8, it shifted 1 position to the left and in 4, 1 position to the right. Post partum, the transitional zone, compared to its ante-partum location, remained at the same lead in 14 instances, whereas in 6, it shifted 1 position to the left and in 5, 1 position to the right.

The Intrinsicoid Deflection.—The intrinsicoid deflection is a rough measure of the time required for the impulse to pass through the segment of ventricular wall beneath the exploring electrode. It was measured from the onset of the QRS complex to the peak of the R wave with the aid of a hand lens. In no instance was the duration of the intrinsicoid deflection longer than 0.05 second. A summary of the actual measurements may be found in Table III.

The S-T Segment in the Precordial Leads.—In V_1, the S-T segment was elevated in 44 per cent of the 75 electrocardiograms used for comparison purposes, in V_2 in 93.3 per cent, in V_3 in 86.7 per cent, in V_4 in 58.7 per cent, in V_5 in 32 per cent, and in V_6 in 21.3 per cent. The degree of elevation was small

and never greater than 1.2 mm., the higher values being observed over the right precordium. The contour of the elevation was concave upward.

In only 1 tracing was the S-T segment depressed. This occurred in V_6 in a tracing taken on the day of delivery in which the S-T segment was depressed 0.5 mm. and was concave upward.

TABLE III. DURATION OF THE INTRINSICOID DEFLECTION (IN SECONDS)

LEAD	ANTE PARTUM			DAY OF DELIVERY			POST PARTUM		
	AVERAGE	MINIMUM	MAXIMUM	AVERAGE	MINIMUM	MAXIMUM	AVERAGE	MINIMUM	MAXIMUM
V_1	0.014	0	0.026	0.013	0	0.020	0.013	0	0.020
V_2	0.014	0.010	0.020	0.013	0.010	0.013	0.014	0.010	0.020
V_3	0.018	0.010	0.030	0.018	0.013	0.030	0.018	0.013	0.026
V_4	0.022	0.013	0.030	0.023	0.020	0.050	0.024	0.013	0.050
V_5	0.024	0.020	0.026	0.025	0.020	0.040	0.025	0.020	0.040
V_6	0.026	0.020	0.040	0.028	0.020	0.040	0.027	0.020	0.040

The T Wave.—In V_1 a positive T wave was noted only once; in the other patients it was usually negative, rarely diphasic or zero. In V_2 it was usually positive, infrequently negative or diphasic. In V_3 it was usually positive, rarely negative or positive diphasic. In V_4 to V_6 the T wave was always positive.

After delivery, the T wave showed varying changes, the direction and extent of which are recorded in Table IV.

TABLE IV. DIRECTION AND EXTENT OF THE T-WAVE CHANGES IN THE PRECORDIAL LEADS ON THE DAY OF DELIVERY AND POST PARTUM IN RELATION TO THE T-WAVE ANTE PARTUM

LEAD	DAY OF DELIVERY							POST PARTUM						
	INCREASE			DECREASE			NO CHANGE	INCREASE			DECREASE			NO CHANGE
	NO.	EXTENT (MM.)	AVERAGE (MM.)	NO.	EXTENT (MM.)	AVERAGE (MM.)		NO.	EXTENT (MM.)	AVERAGE (MM.)	NO.	EXTENT (MM.)	AVERAGE (MM.)	
V_1	8	0.2-1.2	0.6	16	0.4-2.1	1.0	1	9	0.1-2.0	0.8	12	0.1-2.8	0.9	4
V_2	6	0.1-2.9	1.6	16	0.2-4.8	1.5	3	15	0.1-4.2	1.7	8	0.2-2.2	1.1	2
V_3	12	0.5-2.1	1.0	11	0.2-3.6	1.0	2	16	0.3-3.3	1.2	7	0.3-0.9	0.5	2
V_4	14	0.1-3.9	1.3	10	0.1-2.4	1.0	1	15	0.1-3.0	1.3	7	0.1-1.5	0.9	3
V_5	15	0.1-4.5	1.6	10	0.1-2.3	0.9	0	16	0.2-3.4	1.0	9	0.2-1.8	0.7	0
V_6	14	0.2-3.1	1.0	9	0.1-1.9	0.5	2	12	0.1-3.0	1.0	8	0.1-1.3	0.6	5

The U Wave.—A U wave was noted in V_1 in 2.7 per cent of the 75 comparative electrocardiograms, in V_2 in 86.6 per cent, in V_3 in 85.3 per cent, in V_4 in 56 per cent, in V_5 in 21.3 per cent, and in V_6 in 6.7 per cent. There was no essential difference in the incidence of the U wave in the various periods. It was usually smallest in V_5 or V_6 and largest in V_2 or V_3. An inverted U wave was never observed.

DISCUSSION

Foremost among the changes in pregnancy which may affect the electrocardiogram is that in the position of the heart. Two factors are important in this respect, either of which is subject to considerable variation, namely, the level of the diaphragm and the configuration of the chest. During pregnancy, the diaphragm may rise from 0 to 4.0 cm., with an average of 1.5 to 2.0 cm.[15] However, the rise may be more apparent than real, for diaphragmatic motion is greater laterally than at the relatively fixed central tendon.[10] Moreover, the effect of the rise will depend to a great extent upon the habitus of the individual.

With advancing pregnancy, there is also a forward displacement of the lower costal cage and abdomen resulting in a lumbar lordosis. That this may affect the position of the heart is not too presumptuous, for chest roentgenograms during pregnancy reveal an encroachment of the heart upon the anterior free space.[4,9]

These positional changes of the heart may become electrocardiographically manifest as a change in the electrocardiographic position or as a change in the mean electrical axis. A shift in the mean axis to the left during the first 2 trimesters of pregnancy and a return to the right in the last trimester have been repeatedly demonstrated.[1,2,4,6] Such a shift was also observed in the majority of cases in this study.

It was of interest to determine whether there was an accompanying change in the electrocardiographic position as defined by Wilson and associates.[22] With advancing pregnancy, this position either remained the same or became slightly less vertical. Late in pregnancy, the heart was usually in the semivertical or intermediate position. Following delivery, again either the position remained the same or became slightly more vertical. In only 1 patient did the electrocardiographic position become less vertical after delivery. In this patient, the heart, semihorizontal before delivery, became horizontal after delivery. This was the only patient whose heart was in a horizontal position. The rarity of this position in normal men below the age of 39 years has been reported.[17]

The change in the mean electrical axis was more pronounced than that in the electrocardiographic position. In many instances, the mean electrical axis changed appreciably with no alteration in the electrocardiographic position. In 1 patient, although the electrocardiographic position of the heart was vertical in the various periods, the direction of the mean electrical axis varied from 86 to 144.5 degrees. In another, although the heart remained semivertical, the axis varied from 51 to 78 degrees.

Although Wilson's method is useful in describing the electrical position of the heart independent of the direction of the mean electrical axis of QRS, the findings indicate that there may be rotation of the heart with no change in the former and considerable change in the latter. Wilson and co-workers[23] have emphasized that a change in the anatomical position of the heart is not necessarily accompanied by a change in its electrocardiographic position. The fact that the transitional zone remained at the same lead after delivery in the majority of tracings indicates, in view of the above observations, that rotation of the heart during pregnancy is principally around its anteroposterior axis.

Those who interpreted the electrocardiographic changes in pregnancy as indicative of cardiac hypertrophy cited as confirmatory evidence the findings on clinical, radiographic, and post-mortem examinations.[3,6] Suffice it to state that this evidence has been questioned by others.[2,4,9,15,20]

From the electrocardiographic viewpoint, ventricular hypertrophy is indicated by a prolonged duration of the intrinsicoid deflection and by an increase in the amplitude of the R wave in the left precordial leads.[8,18] In this study, both the intrinsicoid deflection and the amplitude of the R wave in these leads were within the limits of normal as determined for nonpregnant individuals.[12,17]

The concept of an "extra heart load" during pregnancy has been invoked by Smith,[16] particularly in regard to the presence of U waves. The high incidence of U waves in normal individuals is to be emphasized.[13,14] An inverted U wave, the only abnormal form yet recognized,[14] was not observed. Furthermore, there was no instance in which the electrocardiographic findings were those of presently accepted "heart strain" patterns.[7,11]

The amplitude of the T wave in the various leads was within the range of values observed in normal nonpregnant individuals.[12,17] Following delivery, the T wave showed varying changes in amplitude in the majority of tracings. For example, the T wave in V_1 and V_2 more frequently decreased than increased, whereas in V_4 to V_6, it more frequently increased than decreased. These changes occurred principally because of a change in the magnitude of the mean T vector rather than in its direction. Similar fluctuations of the T wave in Lead 5 were found by Thomson and associates.[19] These primary T-wave changes are probably related to the various systemic biochemical alterations occurring during pregnancy and the puerperium and not to intrinsic myocardial disease.

SUMMARY AND CONCLUSIONS

1. Ninety-eight electrocardiograms of 25 normal patients with uncomplicated pregnancy, delivery, and post-partum course were studied. Electrocardiograms were taken ante partum, within 24 hours following delivery, and during the early puerperium.

2. With advancing pregnancy, the electrocardiographic position of the heart either remained the same or became less vertical. Following delivery, it either remained the same or became more vertical. A horizontal position was not observed during pregnancy; however, it was present in 1 patient after delivery.

3. The mean electrical axis shifted to the left with advancing pregnancy until the latter part of the third trimester, when it usually shifted toward the right. The shift to the right continued after delivery.

4. The direction of the mean electrical axis of QRS may change even though the electrocardiographic position of the heart remains the same.

5. The major positional change of the heart during pregnancy and the puerperium is rotation around its anteroposterior axis.

6. There were no electrocardiographic manifestations of ventricular hypertrophy or "strain."

7. After delivery, changes in the amplitude of the T wave, due principally to changes in the magnitude of the mean T vector rather than in its direction, were observed.

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COMPLETE HEART BLOCK IN PREGNANT WOMEN

Review of the Literature

Elwyn Evans, M.D., and Louis Pohlman, M.D.

Orlando, Fla.

COMPLETE heart block is rare in pregnant women. Hamilton and Thompson[1] at Boston Lying-in Hospital reported 2 cases of complete heart block in 850 cardiac patients and 43,190 deliveries. Mitchell and associates[2] found 1 case in 17,862 deliveries at Kings County Hospital.

Because of the rarity of complete heart block in pregnancy and some confusion in the literature, it was thought that this case should be reported and the literature again reviewed.

CASE REPORT

Mrs. H. L. L., 17 years old, was seen on April 11, 1947, because of pregnancy complicated by heart disease. A "leaky heart" and a slow pulse were known since childhood. She previously had had a normal delivery, the child surviving. She was now 2 months pregnant. The only symptom was exertional dyspnea which appeared shortly before she became pregnant. The dyspnea was most noticeable when she was nervous. There was no history of chorea, rheumatic fever, or syphilis. The past and family histories were not significant.

Physical examination revealed a somewhat nervous young woman. The blood pressure was 104/56 mm. Hg. The pulse was regular at 35 per minute. The left border of cardiac dullness and the point of maximal apical impulse were 8.5 cm. to the left of the mid-sternal line in the fourth intercostal space at the mid-clavicular line. A Grade 3 plus systolic murmur could be heard over most of the chest anteriorly, maximal in the third to fourth intercostal spaces, a little farther to the left than usually heard in patients with interventricular septal defects, but poorly heard in the left axilla and back. The second pulmonic sound was greater than the second aortic sound. The lungs were clear. The neck vessels were not abnormal. The liver was not palpable, and there was no edema of the extremities.

Fluoroscopy of the chest revealed clear lung fields. The heart was normal in size and shape. Orthodiagraphic measurements were $\frac{T}{TH} = \frac{9.5}{20}$ cm. The electrocardiogram showed complete heart block but was not otherwise abnormal (Fig. 1).

A diagnosis of complete heart block, probably congenital, probable interventricular septal defect, and pregnancy was made. The patient was reassured and advised to continue with the pregnancy.

The patient was not seen again until Dec. 10, 1948, when she gave a history of having delivered a normal 6 pound 4 ounce boy spontaneously without difficulty on Sept. 6, 1947. She was again 6 weeks pregnant. There was some exertional dyspnea but no other symptoms referable to the heart. The left border of cardiac dullness was 9 cm. to the left of the mid-sternal line 0.5 cm. outside the mid-clavicular line. The lungs were clear and there was no pitting edema. Orthodiagraphic measurements were $\frac{T}{TH} = \frac{10.1}{19.7}$ cm. The electrocardiogram (Fig. 2) showed definite progressive changes since the first tracing.

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Because of the dypsnea, slight increase in heart size, and progressive electrocardiographic changes, pregnancy was terminated by hysterotomy and the patient was sterilized.

DISCUSSION

To date, 25 patients with complete heart block in pregnancy,[1-22] including ours, have been reported. Three besides our patient were seen in 2 pregnancies after heart block was diagnosed.[17,19,22] Herrmann and King's[7] patient was known to have survived 6 pregnancies spontaneously. The number of pregnancies complicating complete heart block is greater because 6 others had had 1 previous pregnancy,[5,9,11,14,20,21] and 1 had had 2 previous pregnancies.[15]

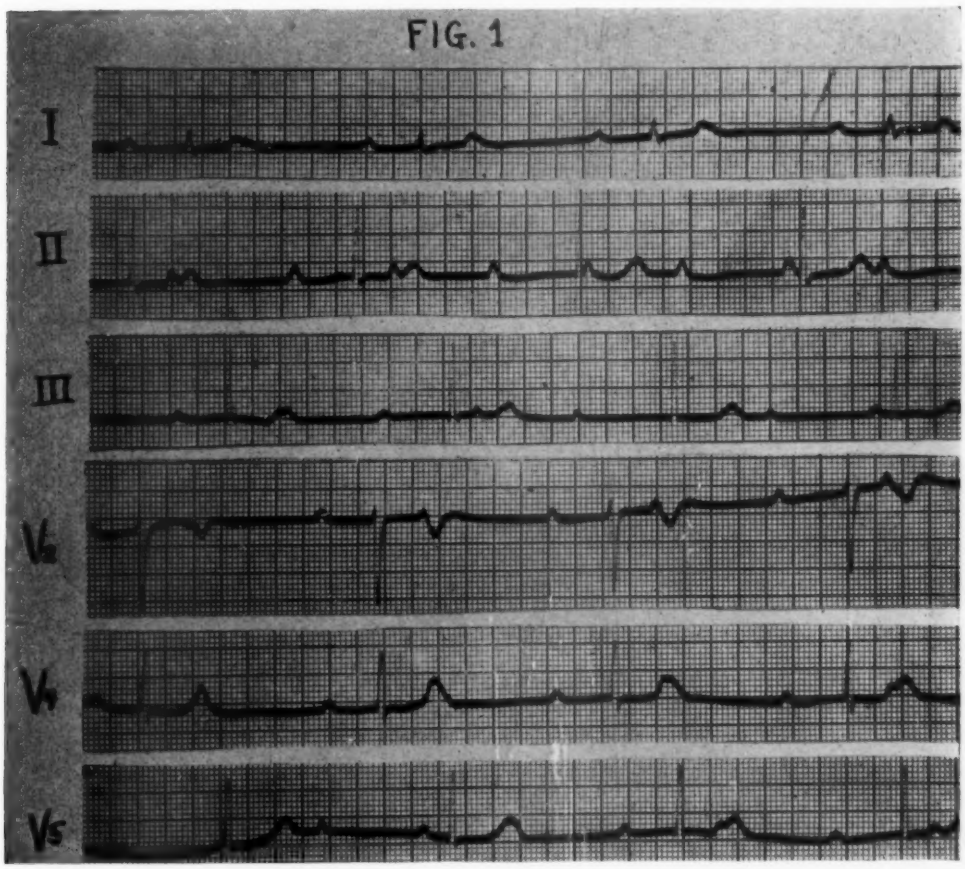

Fig. 1.--April 11, 1947.

Our criteria were rigid, so some reported cases were not included in this series, although they are described in the discussion. A slow pulse alone was not acceptable; electrocardiograms were required in accepted cases. No other definite clinical evidence of complete block was presented in the discarded cases. None of the patients in whom heart block was known to have appeared for the

first time after delivery or who had partial or incomplete block were considered cases of complete heart block in pregnancy.

Greenhill[10] stated that it was not uncommon to see heart block during pregnancy, labor, or in the puerperium in women who do not have it at other times, but Jensen[13] stated that this was not the general experience.

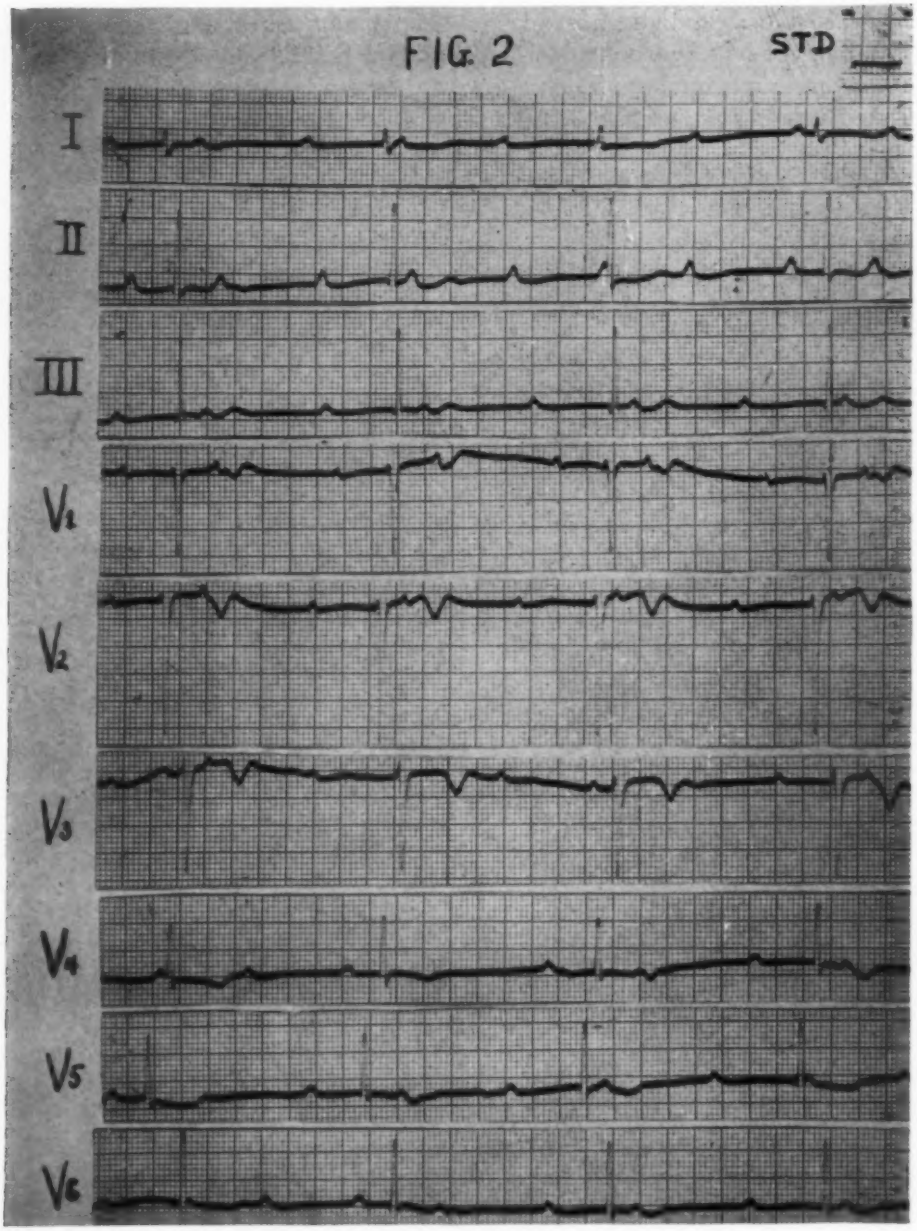

Fig. 2.—Dec. 10, 1948. Note the RS-T and T changes in the left precordial leads since April 11, 1947.

The first acceptable case of complete heart block in a pregnant woman was reported by Walz[3] in 1922. Freund,[23] in 1917, had described a patient with a slow pulse, but no electrocardiogram was taken. The patient died 1 and ½ hours after delivery, and an autopsy revealed acute and chronic endocarditis. Several investigators, including Walz[3] and Dressler,[5] did not believe Freund presented sufficient evidence to warrant making the diagnosis of complete heart block. Jensen[13] stated that Nest mentioned 3 cases but did not give evidence to support the diagnosis. Langley[24] mentioned a case but did not describe it. Case 3, reported by Clerc and Levy,[6] previously reported by Jeannin and Clerc,[25] had 2:1 block, and Case 4, included in our series, had complete heart block alternating with partial heart block. Laubry, in discussing the paper of Jeannin and Clerc, mentioned a patient he had seen but stated that the case was not well studied; no electrocardiogram was taken. Electrocardiographic findings were not mentioned in Naujoks' paper.[26] Herskovic's[27] patient was not known to have a slow pulse until 15 minutes after delivery, shortly before death. The pulse was 84 during labor. Autopsy revealed an abscess of the auriculoventricular node. Hamilton and Thompson[1] described 2 cases, one of which was previously reported by Titus and Stevens,[8] and mentioned a third patient seen during the puerperium of her third pregnancy. The latter was not included in our series. All pregnancies had been uneventful, and all patients were thought to have congenital heart disease. Electrocardiograms were not mentioned by Hamilton and Thompson,[1] but they were taken.[28] Bramwell's[29] patient had rheumatic heart disease with mitral stenosis and partial heart block and died 2 hours post partum. Naish[30] described 2 patients, the first previously reported by McIlroy and Rendel,[9] each successfully going through two pregnancies, but he did not mention electrocardiograms. Jensen[13] stated that the electrocardiogram of Greenhill's[10] patient was turned around to represent a mirror image of the usual tracing and really showed a 2:1 block with prolonged auriculoventricular conduction. The tracing does appear to have been turned around, but the P waves have no definite relation to the QRS complexes. Sigler's[11] patient, at first, had alternating complete and partial heart block and later developed 2:1 block with prolonged auriculoventricular conduction. Otto[31] gave a patient strophanthin during collapse at the beginning of delivery; heart block occurred in steps starting 5 hours after delivery and lasted until death 7 hours later. Autopsy revealed slight hypertrophy of the left ventricle.

Of the 25 acceptable cases of complete heart block during pregnancy, 14 were multipara. The ages ranged from 15 to 38 years with an average of 26 years. Seven were thought to be of rheumatic cause, 1 syphilitic, 3 infectious, 3 unknown, and 11 congenital (5 and possibly 7 of whom were thought to have interventricular septal defects). Of the 7 patients with rheumatic heart disease, 5 had mitral insufficiency and 2 of these had mitral stenosis. Lesions were not described in the remaining 2 cases. One of the 2 patients with double mitral lesions also had auricular fibrillation, but no enlargement. Only 2 of the patients with mitral insufficiency showed enlargement.

Two patients had precordial pain alone, another precordial pain and syncope, 5 syncope only, 2 dizziness, 3 fatigue, palpitation, and dyspnea, and 1 dyspnea only. The heart was enlarged in 11, slight in 6 of these. Marked cardiac enlargement was not mentioned; however, 1 patient was described as having enlargement to the right and left. Only 3 of the 11 patients with cardiac enlargement had symptoms referable to the heart and these had precordial pain. Of 7 patients with symptoms of possible cardiac origin, only 3 showed cardiac enlargement and these had precordial pain.

Although pain in heart block in general was thought to be of serious import,[15] it did not affect the mortality rate in the group with complete heart block during pregnancy because all of the 24 patients reaching term survived. Neither did cardiac enlargement nor dyspnea affect the mortality. According to Hamilton and Thompson,[1] no sharp line between enlarged and normal hearts can be drawn in pregnant patients, and in a great majority of the cases, the heart only appears enlarged because of changes in heart position.

Fifteen of the 25 patients with complete heart block delivered spontaneously. Four of the remaining 10 were delivered by forceps and 4 by cesarean section. One was delivered by podalic version and breech extraction from left shoulder presentation. The puerperium was normal in all. Accurate data concerning the fetus were not obtainable, but fetal death was apparently rare.

SUMMARY AND CONCLUSIONS

1. A case in which a second uneventful pregnancy terminated spontaneously in a patient with pre-existing complete heart block, probably congenital, is presented and the literature reviewed. A third pregnancy was interrupted at 2 months because of increased dyspnea and heart size and definite progressive electrocardiographic changes.

2. Complete heart block in pregnancy is not a contraindication to pregnancy; in fact, these patients do remarkably well.

3. Termination of pregnancy must be based on the usual indications, not the heart block per se.

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SPATIAL VECTORCARDIOGRAPHY: MYOCARDIAL INFARCTION. V.

LEONARD SCHERLIS, M.D., AND ARTHUR GRISHMAN, M.D.

NEW YORK, N. Y.

WITH THE COOPERATION OF AVERY A. SANDBERG, M.D.

THE QRS complex of the electrocardiogram represents the summation of innumerable electromotive forces generated by the wave of accession in diverse areas of the myocardium. These multiple electromotive forces vary in magnitude and differ in direction. At any one instant, the resultant of these electromotive forces can be represented by a spatial vector which has magnitude, direction, and sense.[1,2] Since the spatial vector is the resultant of diverse forces, it is altered by any factor which decreases or increases the magnitude of any of the component electrical forces or alters their direction. Uncomplicated rotation or displacement of the heart will therefore alter the orientation of the spatial vector. Hypertrophy, on the other hand, will not only alter the orientation in space of the vector because of accompanying rotation, but may also affect the magnitude of the spatial vector.

Myocardial infarction with destruction of large areas of ventricular muscle will result in the loss of the electromotive forces normally present in that area during the process of accession. Hence, because of the loss of these forces, the resultant spatial vector will be altered in magnitude and direction because of unbalanced forces arising from intact portions of ventricular muscle.[1,2,3]

This alteration is usually recorded by electrocardiograms taken in a plane representing the projection onto this plane of the new spatial vector. The orientation and magnitude of this resultant vector is thought to depend upon the size and location of the infarcted area.

Vectorial analyses of the electrocardiograms in the frontal plane have been made by Mann,[4] who subsequently published vector loops recorded with the aid of special apparatus.[5] The introduction of the cathode ray oscillograph simplified the recording of the vectorcardiogram in the frontal plane,[6] and later this method was applied to the determination of the spatial vectorcardiogram. The application of spatial vectorcardiography to the study of myocardial infarction has been made by Duchosal and Sulzer,[7] Vastesaeger,[3] and others utilizing various methods of spatial representation.

In the present study, the vectorcardiograms in the horizontal, sagittal, and frontal planes were recorded simultaneously. This technique provides an excellent method for the determination of the spatial distribution of electromotive forces in myocardial infarction. Since routine electrocardiographic

From the Department of Cardiography and the Cardiovascular Research Group, The Mount Sinai Hospital, New York.

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leads may not record evidence of infarction, an analysis of spatial vectorcardiograms may provide further aid in the electrocardiographic diagnosis of infarction. Esophageal electrocardiograms and multiple thoracic leads were also utilized in order to correlate the patterns obtained in the vectorcardiograms with those in the conventional electrocardiograms.

METHODS

The group of patients included in this study consisted of sixty-seven persons with electrocardiographic evidence of myocardial infarction. The electrocardiographic criteria for the selection of these cases were essentially those of Wilson and co-workers.[8] In every instance, there was a typical clinical course and history of a myocardial infarction. The patients were divided into the following groups:

1. Forty-one persons with infarction of the diaphragmatic or inferior aspect of the heart as determined by an abnormal Q wave (25 per cent or more of the R wave) in Lead V_F. Twenty-one persons of this group had additional electrocardiographic evidence of infarction of the anteroseptal, anterolateral, posterior, or localized anterior aspect of the heart.

2. Sixteen persons with localized infarction of the anteroseptal aspect of the heart as determined by the presence of prominent Q waves in V_1 and V_2 and extending in some instances as far as V_4. Three of these persons had additional electrocardiographic evidence of infarction of the inferior aspect of the heart.

3. Fifteen persons with infarction of the anterolateral aspect of the heart as evidenced by prominent Q waves in Leads V_4, V_5, and V_6, or V_5 and V_6, or V_6 alone. Ten of these persons had additional electrocardiographic evidence of infarction of the inferior or anteroseptal aspect of the heart.

4. Nine persons with well-localized infarction of the anterior aspect of the heart as evidenced by prominent Q waves in V_2, V_3, V_4, or V_5 or in any adjacent two or three of these leads without prominent Q waves in Lead V_6. Four of these persons had additional evidence of infarction of the inferior aspect of the heart.

5. Nine persons with presumptive infarction of the posterior aspect (as distinguished from the diaphragmatic or inferior aspect) of the heart. The selection of this group is more fully explained in the results. Six of these persons had, in addition, infarctions of the inferior, or anterolateral, aspect of the heart, while three others had no definite electrocardiographic evidence of infarction at the time of recording the vectorcardiograms. The latter three patients, however, did have a typical history and clinical course of infarction and serial electrocardiographic changes indicative of previous myocardial infarction.

Standard, unipolar extremity, six unipolar precordial, and multiple thoracic leads were recorded for each patient. Esophageal electrocardiograms were also recorded at fifteen levels in eleven patients. The method used in recording multiple esophageal electrocardiograms has been given in detail elsewhere.[9]

Vectorcardiograms were then recorded utilizing, in principle, the method of Duchosal and Sulzer.[7] The details of the method employed in the present study are being reported separately.[10] The vectorcardiograms in the horizontal,

sagittal, and frontal planes were simultaneously visualized on a Tri-Beam Technicon Scope and photographed on one film. The direction of rotation of the cathode ray beam was noted and recorded for each plane by several observers, and motion pictures were occasionally taken. Wherever "right" or "left" is used in the description of the orientation of the loop, the reference is to the patient's right or left.

An electrical tuning fork with a frequency of 400 cycles per second interrupted the recording of the beam each 0.0025 second and thus permitted a time analysis of the record.

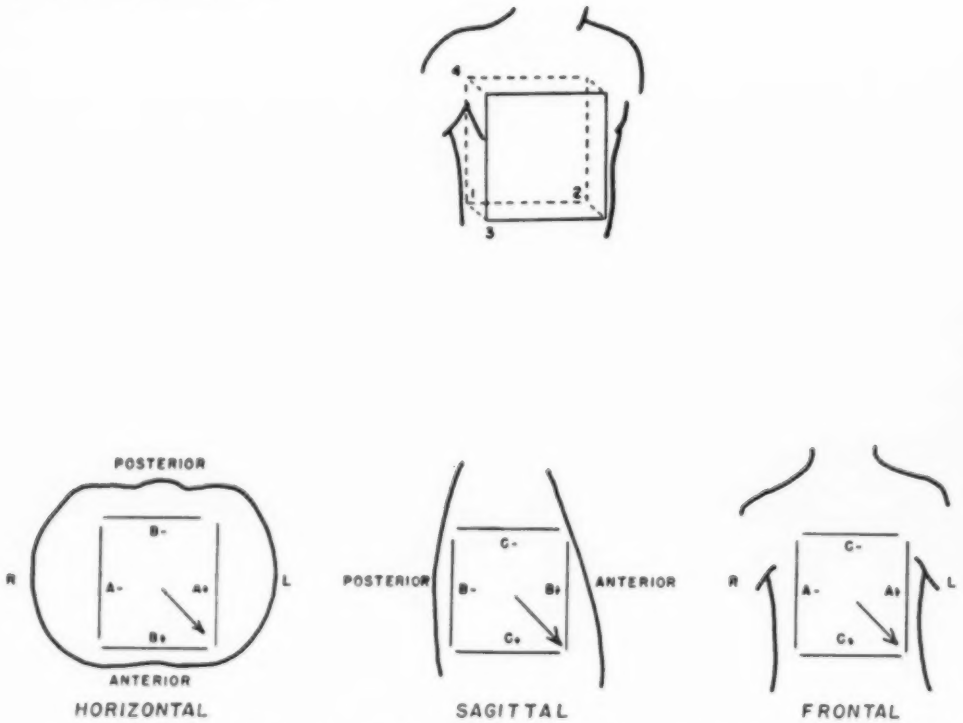

Fig. 1.—In the upper figure each number refers to the location of the electrodes as placed upon the thorax. The *A*−, *B*−, and *C*+ electrodes are placed at location *1*: *A*+ at *2*; B+ at *3*; and *C*− at *4*. The three projections of the spatial vectorcardiograms utilized in the present study are shown in the lower figures. The arrow points in the direction of positivity for the movement of the beam when the plates of the cathode ray oscillograph are connected as indicated.

For the simultaneous recording of the spatial vectorcardiogram in each of three planes, three pairs of electrodes were utilized: A (horizontal), B (sagittal), and C (vertical) (Fig. 1). The placement of electrodes was as follows:

1. *A*−, *B*−, *and C*+: a common electrode, located at about the level of the second lumbar vertebra in the right posterior axillary line.
2. *A*+: at the level of the second lumbar vertebra in the left posterior axillary line (i.e., at the same level as 1).
3. *B*+: over the lower rib margin in the right anterior axillary line (i.e., in the same plane as 1 and 2).

4. *C*−: over the right shoulder posteriorly (i.e., in the same plane as 1 and 3).

These locations may be considered as representing four of the corners of a cube.

The components of the horizontal plane were thus recorded by the A and B electrodes; of the sagittal, by B and C; and of the frontal, by A and C. The introduction of 1 mv. into this circuit was represented in each plane by the movement of the cathode ray beam at a 45 degree angle downward and to the patient's left (Fig. 1). The standardization employed was the same in each plane and was recorded in simultaneous electrocardiograms representing the three pairs of electrodes.

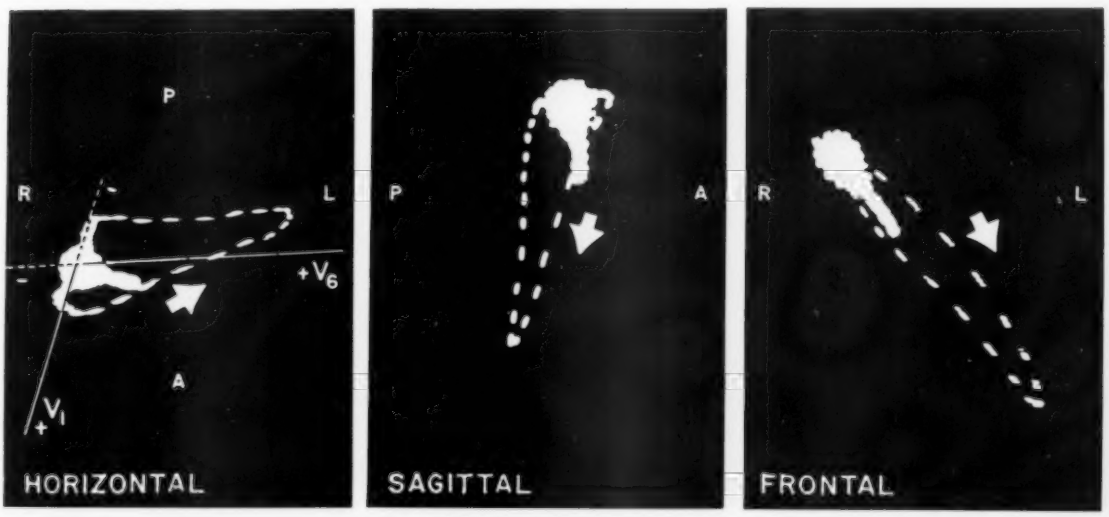

Fig. 2.—Normal vectorcardiogram. The larger loop is the QRS sÊ loop; the smaller is the T sÊ loop. The loops are photographed simultaneously for the three planes, and each portion of the loop represents 0.0025 second. V_1 and V_6 in the horizontal plane represent the approximate axes for the derivation of these leads. The solid line represents the positive axis of projection; the interrupted line represents the negative axis of projection. (*R* = right, *L* = left; *P* = posterior, *A* = anterior; the arrow indicates the direction of inscription for each loop. The orientation of the loops is similar in all subsequent figures.)

RESULTS

In a normal person without any electrocardiographic or clinical evidence of myocardial infarction, conduction delay, or heart disease, the QRS sÊ loops of the spatial vectorcardiograms are characterized by the essentially even spacing of the interrupted segments of the vector loops. In the horizontal plane, the QRS sÊ loop is initiated by a small deflection anteriorly and usually to the patient's right, followed by the smooth inscription of the loop in a counterclockwise direction to the left and in a posterior direction. In the sagittal plane, the loop is inscribed in a clockwise direction and may begin with an initial small deflection anteriorly before the major inscription inferiorly and posteriorly. In the frontal plane, the direction of the inscription of the QRS sÊ loop may be in a clockwise or counterclockwise direction. Where there is no axis deviation

or a tendency to right axis deviation, the loop is inscribed downward in a clockwise direction and somewhat to the patient's left (Fig. 2). Where there is a tendency to left axis deviation, the loop is inscribed downward, still more to the patient's left, and usually in a counterclockwise direction. The variability of the normal spatial vectorcardiogram will be discussed in a later publication.

For the purpose of discussion, the findings in the various types of infarction are presented separately; however, it should be noted that the interruptions of the QRS sÊ loop by the time marker revealed no definite evidence of conduction delay in any case, the segments being fairly regularly spaced. (Only the QRS sÊ loop is discussed, since an analysis of the T wave and RS-T segment is under preparation.)

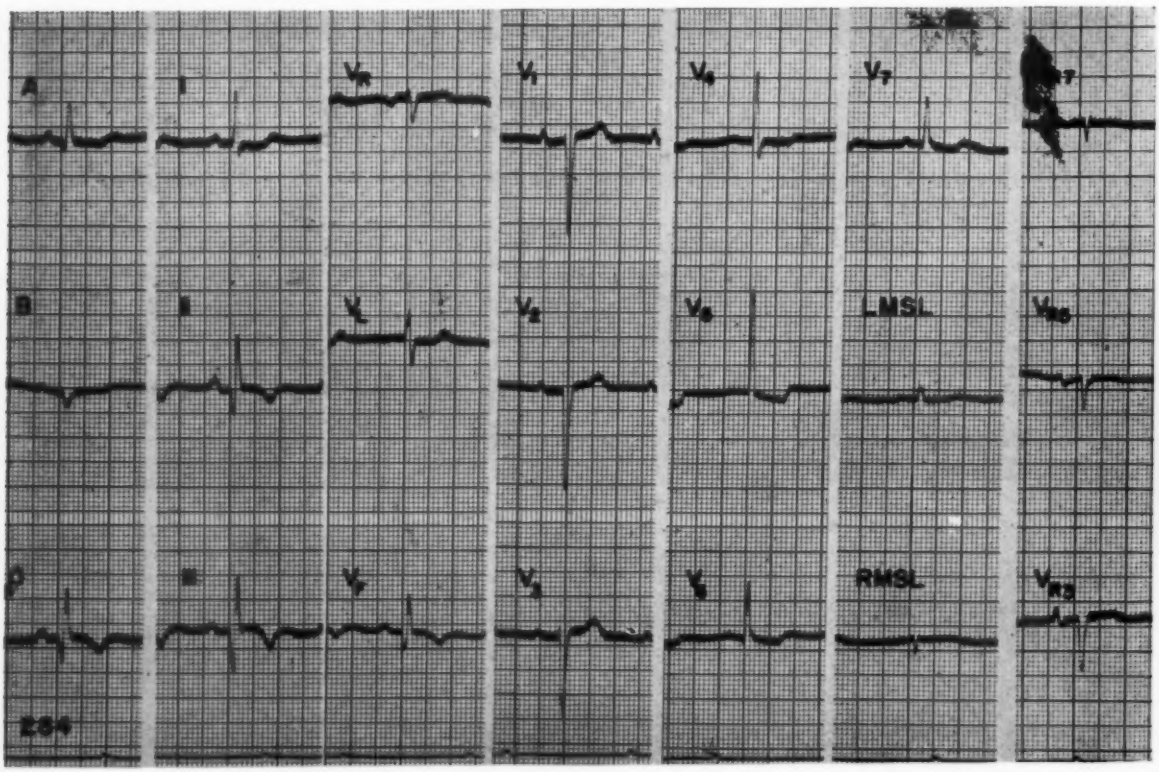

Fig. 3*A*.—Diaphragmatic or inferior infarction. Note the significant Q wave in II, III, and V_F. (*A*, horizontal component; *B*, sagittal component; *C*, vertical component. V_7: left posterior axillary line; *LMSL*: left mid-scapular line; *RMSL*: right mid-scapular line; V_{R7}: right posterior axillary line; V_{R5}: right anterior axillary line; and V_{R3}: medial to right mid-clavicular line, are all recorded at the level of V_6.)

1. *Infarction of the Diaphragmatic or Inferior Aspect of the Heart.*—In the twenty persons with electrocardiographic evidence of infarction of the inferior aspect of the heart without significant Q waves in the precordial leads, the QRS sÊ loops in the horizontal plane were essentially normal in contour and orientation and were inscribed in a counterclockwise direction.

The QRS sÊ loops in the sagittal plane were characterized by the initial inscription of the loop in an upward direction. After the inscription of the initial portion of the loop, the beam often continued upward as the loop was inscribed in a counterclockwise direction or, more rarely, came downward as the loop was inscribed in a clockwise direction. In each instance, a greater than normal portion of the loop was initially inscribed in an upward direction. In two instances, the loop was "figure 8" in configuration with the initial loop inscribed in an upward direction. The loops in this plane were often displaced in a markedly upward direction and were usually inscribed in a counterclockwise rather than a clockwise direction (Figs. 3*A* and 3*B*).

In the frontal plane, the QRS sÊ loops were often displaced markedly upward. The initial deflection was upward and in all but two of the instances to the patient's left and was inscribed in a clockwise direction.

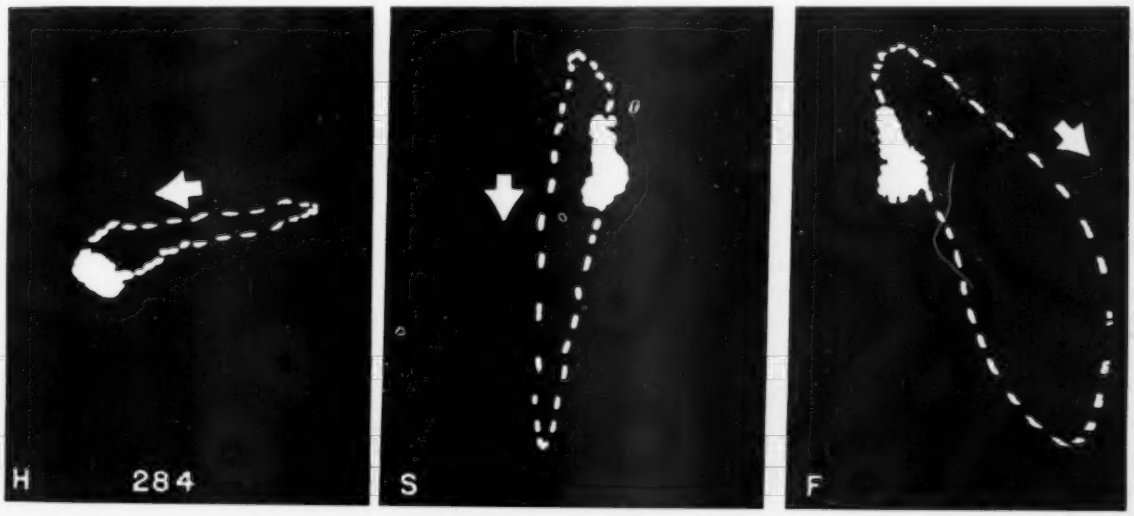

Fig. 3*B*.—Vectorcardiogram No. 284 (same case as Fig. 3*A*; *H*, horizontal plane, *S*, sagittal plane, *F*, frontal plane). The horizontal plane QRS sÊ loop is essentially unaltered while the initial portions of sagittal and frontal plane QRS sÊ loops are displaced upward. The sagittal plane QRS sÊ loop is inscribed in a counterclockwise direction.

In the remaining twenty-one persons with electrocardiographic evidence of infarction of the inferior aspect of the heart, there was also evidence of infarction of the anteroseptal, anterior, posterior, or anterolateral aspects of the heart. The QRS sÊ loops in the horizontal plane were altered as described in the following results under the appropriate heading. In the sagittal plane, the QRS sÊ loops, in addition to the alterations already described, were often displaced in a markedly posterior direction. In the frontal plane, the QRS sÊ loops were initially inscribed upward and usually to the patient's left in a clockwise direction. At times, the loop was inscribed to the patient's right and continued in a clockwise or counterclockwise direction.

Multiple esophageal leads were recorded in eleven of the patients with inferior or diaphragmatic infarctions and were characterized by QR or QS patterns

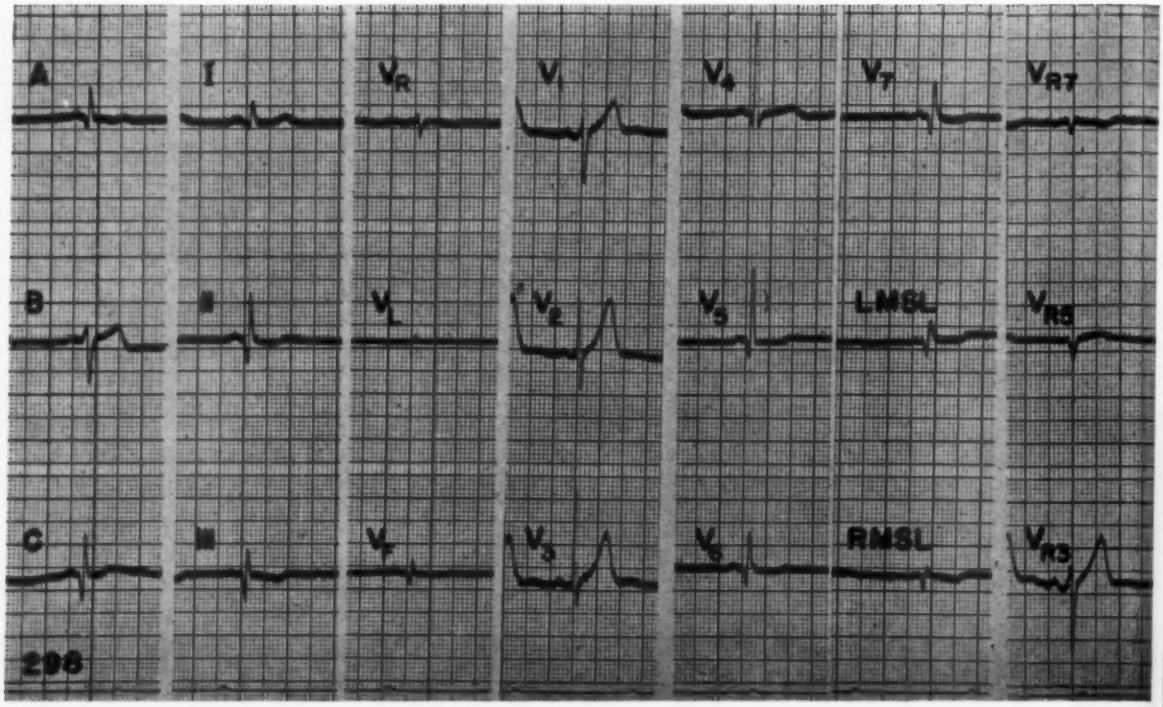

Fig. 4*A*.—Diaphragmatic and anterolateral infarction. Note the significant Q wave in II, III, V_F, and V_6.

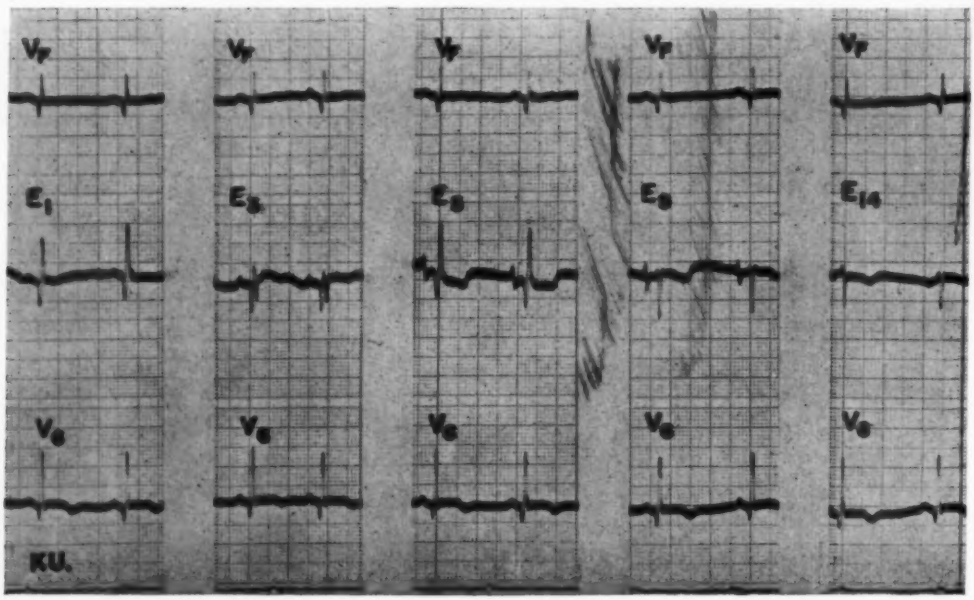

Fig. 4*B*.—Esophageal electrocardiograms (same case as Fig. 4*A*). E_1 and E_3 are recorded at lower esophageal levels; E_5 and E_9 at left atrial level, as evidenced by intrinsic atrial deflections; and E_{14} at a supracardiac level. Note the similarity of V_F and E_1.

in lower esophageal leads (E_1 to E_5) (Figs. 4*A*, 4*B*, and 4*C*). E_1 in each instance was essentially similar to V_F. In those instances where the esophageal leads recorded essentially upright deflections at supracardiac levels, the QRS sÊ loops were deviated in an upward direction as recorded in the sagittal and frontal plane vectorcardiograms (Figs. 5*A*, 5*B*, and 5*C*).

2. *Infarction of the Anteroseptal Aspect of the Heart.*—In the vectorcardiograms of the thirteen persons with electrocardiographic evidence of infarction confined to the anteroseptal aspect of the heart, the horizontal plane QRS sÊ loops were characterized by the loss of the initial deflection anteriorly to the patient's right. The QRS sÊ loops were inscribed sharply posteriorly and to the patient's left. The loops were inscribed in a counterclockwise direction in all but two instances (Figs. 6*A* and 6*B*).

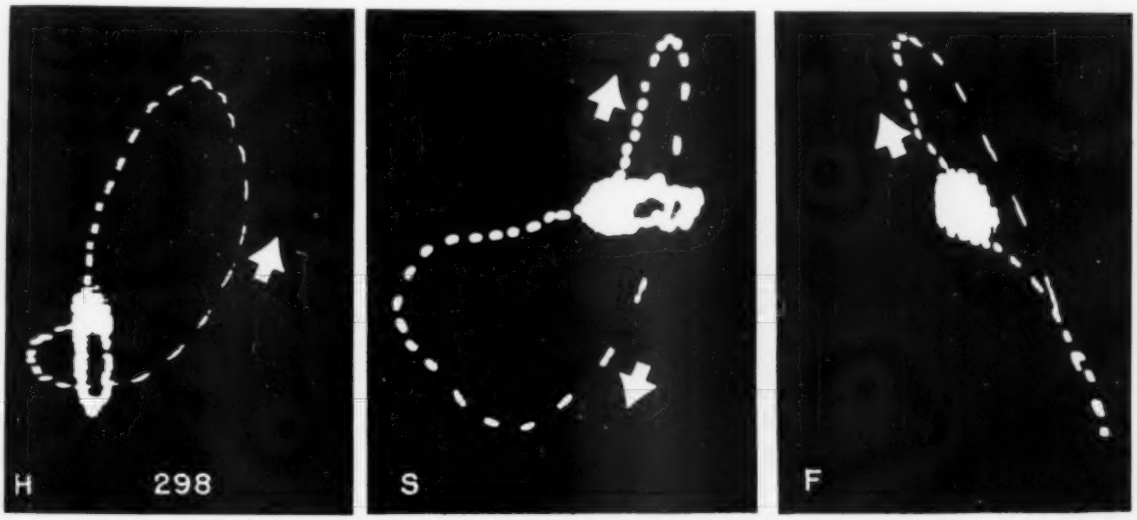

Fig. 4*C*.—Vectorcardiogram No. 298 (same case as Figs. 4*A* and 4*B*). The initial deflection to the right is increased in the horizontal plane. The sagittal plane QRS sÊ loop is displaced upward, and the frontal plane loop is initially displaced upward and to the right.

In the sagittal plane, the QRS sÊ loops lacked the initial small anterior deflection and were often deviated in a posterior direction. Otherwise, the loops remained unaltered in this plane and were inscribed in a clockwise direction.

The frontal plane QRS sÊ loops were usually unaltered. Occasionally, the initial deflection was to the patient's right rather than to the left, when significant Q waves were present in standard lead I.

In the vectorcardiograms of the remaining three persons with anteroseptal infarction, there was also electrocardiographic evidence of infarction of the inferior aspect of the heart. The horizontal plane QRS sÊ loops remained as described in uncomplicated anteroseptal infarction. The QRS sÊ loops in the sagittal plane were displaced upward and posteriorly and were inscribed in a counterclockwise direction (Figs. 7*A* and 7*B*). The initial deflection in this plane was upward. In the frontal plane, the QRS sÊ loops were often displaced in an upward direction and were often inscribed upward in a clockwise direction and to the patient's left.

3. *Infarction of the Anterolateral Aspect of the Heart.*—In the vectorcardiograms of the five persons with electrocardiographic evidence of infarction localized to V_4, V_5, and V_6, or V_5 and V_6, or V_6 alone, the QRS sÊ loops in the horizontal

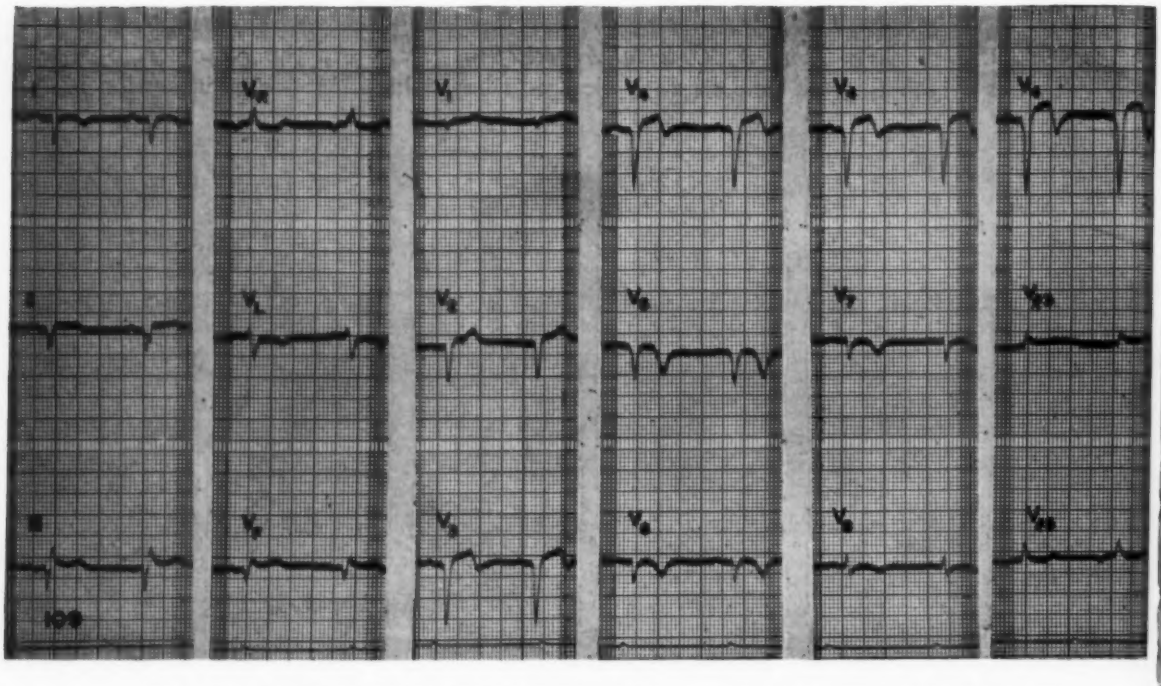

Fig. 5*A*.—Diaphragmatic and extensive anterior infarction. Note the prominent Q wave in II, III, V_F, and V_2 to V_5 and the prominent R wave in V_R, V_{R3}, and V_{R5}.

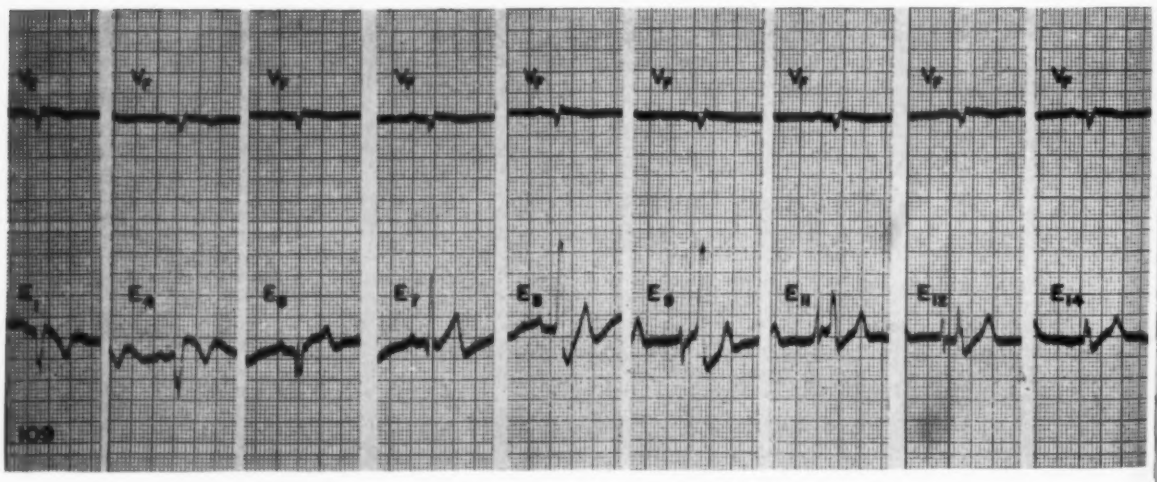

Fig. 5*B*.—Esophageal electrocardiograms (same case as Fig. 5*A*). E_1 and E_4 are recorded at lower esophageal levels; E_9 and E_{12} at atrial level, as evidenced by the presence of an intrinsic atrial deflection; and E_{14} at a supracardiac level. Note the similarity of V_F to E_1, the negative QRS deflection in E_1 and E_6, and the upright QRS deflections from E_8 to E_{14}.

plane were characterized by the initial inscription of a deflection anteriorly and to the patient's right, followed by the inscription of the major portion of the loop in a counterclockwise direction sharply posteriorly and to the right, or a continuation of the loop in a clockwise direction to the right (Figs. 8*A* and 8*B*). In either instance, the initial portion of the loop was deviated to the patient's right. In the sagittal plane the QRS sÊ loops appeared to be of normal configuration and orientation, being inscribed in a clockwise direction. The frontal plane QRS sÊ loops were, in two instances, initially inscribed to the patient's right and then continued in a counterclockwise direction downward and to the patient's left. In the other two, the QRS sÊ loops were inscribed downward and to the patient's left, in a counterclockwise direction without any initial deviation to the right.

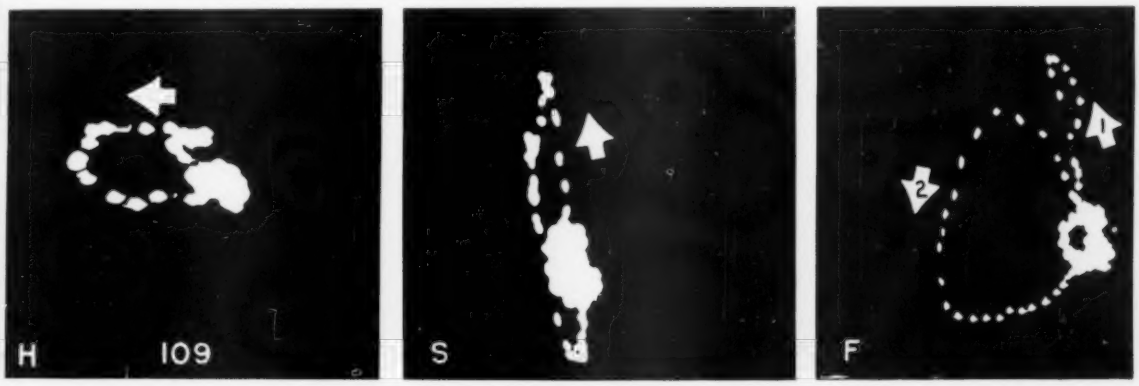

Fig. 5*C*.—Vectorcardiogram No. 109 (same case as Figs. 5*A* and 5*B*). The horizontal plane loop is displaced markedly to the right and somewhat posteriorly. The sagittal plane loop is displaced markedly in an upward direction, and the frontal plane loop is displaced upward and to the right. (In the frontal plane the initial portion of the loop is on the patient's left.)

In ten instances of infarction of the anterolateral aspect of the heart, there was also infarction of the inferior aspect of the heart as evidenced by prominent Q waves in V_F (Figs. 9*A* and 9*B*). The QRS sÊ loops in the horizontal plane were as described for uncomplicated anterolateral infarction, six of the loops being inscribed in a clockwise direction and four in a counterclockwise direction. The QRS sÊ loops in the sagittal plane were as described for uncomplicated infarction of the inferior aspect of the heart. In the frontal plane, the QRS sÊ loops were initially inscribed in an upward direction, going to the patient's right and then continuing in a clockwise direction upward and to the patient's left in five, and in a counterclockwise direction downward and to the right in four others. In one instance, the loop was inscribed in a counterclockwise direction upward and to the patient's right.

4. *Localized Infarction of the Anterior Aspect of the Heart.*—In the vectorcardiograms of three of the five persons with electrocardiographic evidence of infarction localized to V_2, V_3, V_4, or V_5, or to any two or three of these leads without prominent Q waves elsewhere, the QRS sÊ loops in the horizontal plane were "figure 8" in configuration with the initial deflection to the left anteriorly

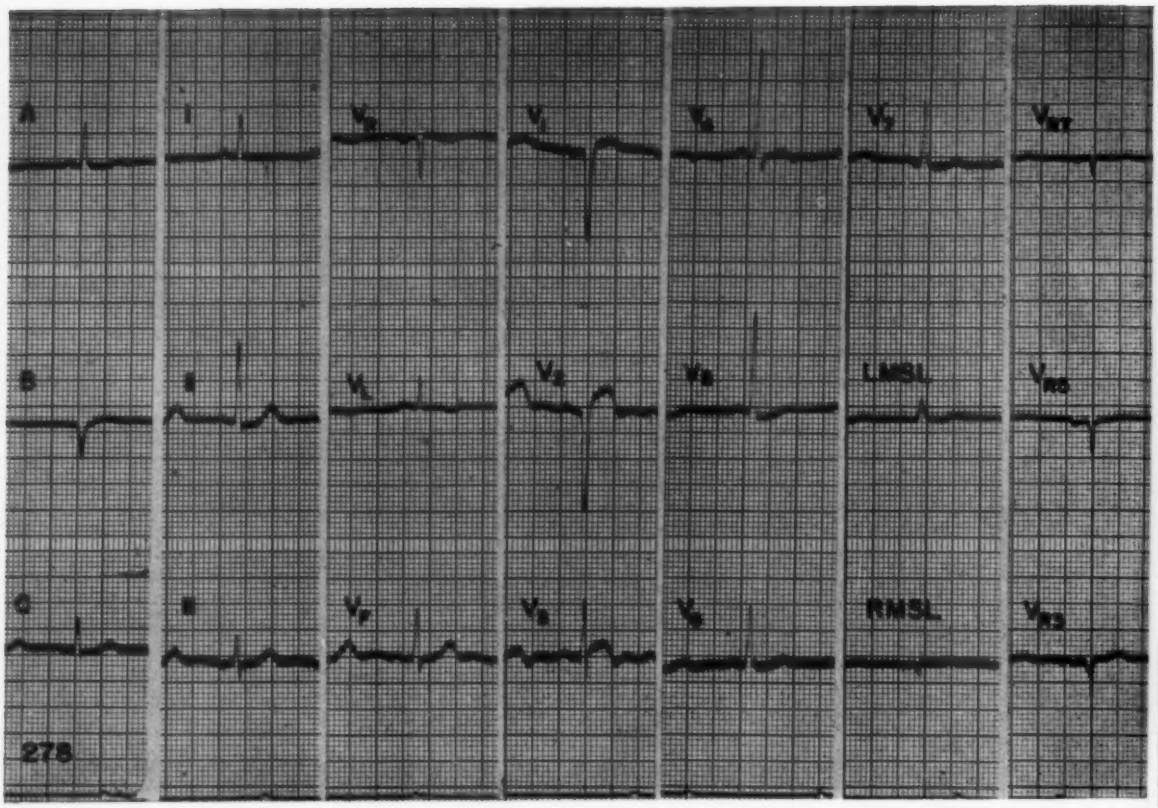

Fig. 6*A*.—Anteroseptal infarction. Note the prominent Q wave in V_1 and V_2.

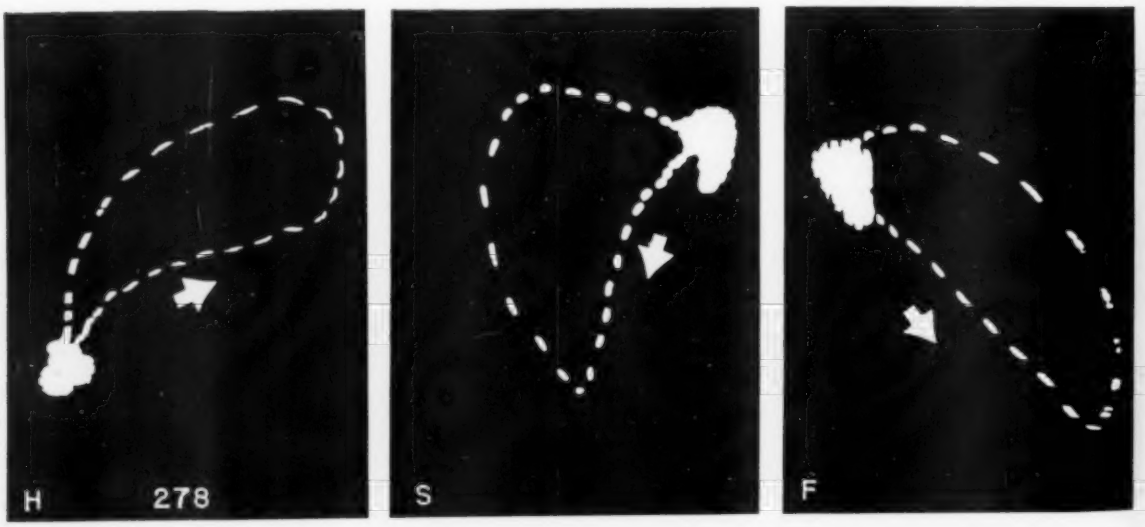

Fig. 6*B*.—Vectorcardiogram No. 278 (same case as Fig. 6*A*). The horizontal and sagittal plane QRS loops are inscribed sharply posteriorly with no initial deflection anteriorly. The frontal plane loop is inscribed in a counterclockwise direction.

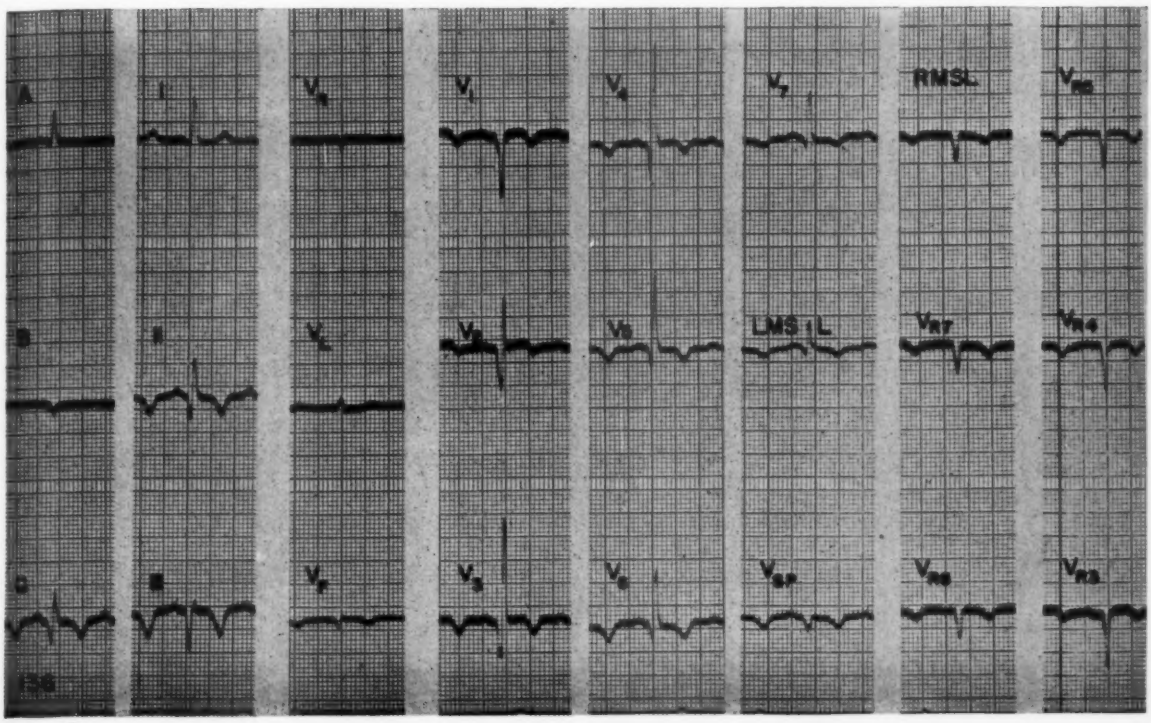

Fig. 7*A*.—Anteroseptal and diaphragmatic infarction. Note the prominent Q wave in II, III, V_F, and V_1 to V_4. (V_{SP}: recorded over vertebral column; V_{R6}: right midaxillary line.)

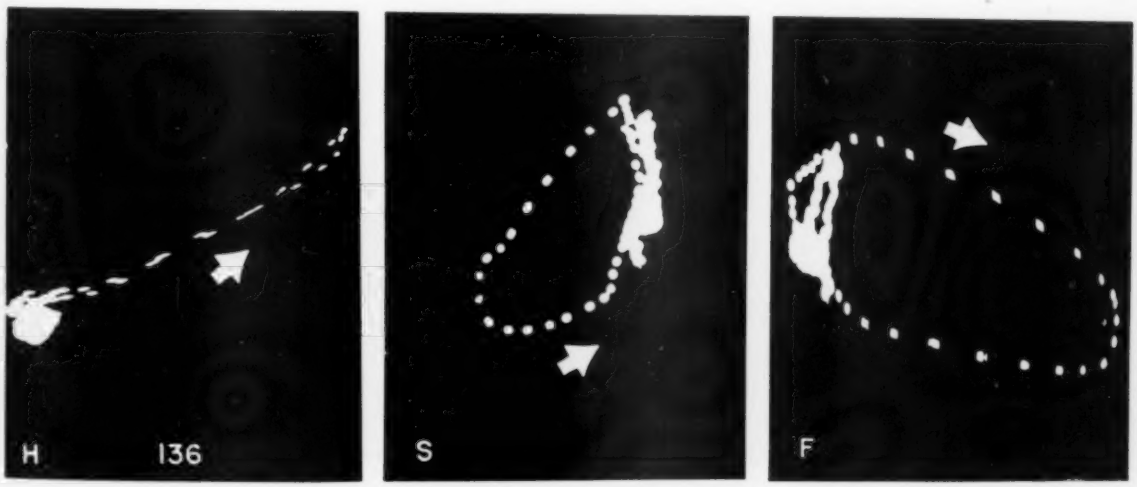

Fig. 7*B*.—Vectorcardiogram No. 136 (same case as Fig. 7*A*). The horizontal plane QRS loop is initially inscribed sharply posteriorly and to the right. The sagittal and frontal plane loops are initially displaced upward with the sagittal loop inscribed in a counterclockwise direction.

being small and followed by a sharp deflection posteriorly and somewhat to the right (Figs. 10*A* and 10*B*). The distal portion of the loop was inscribed in a clockwise direction with the centripetal limb being inscribed to the right. In

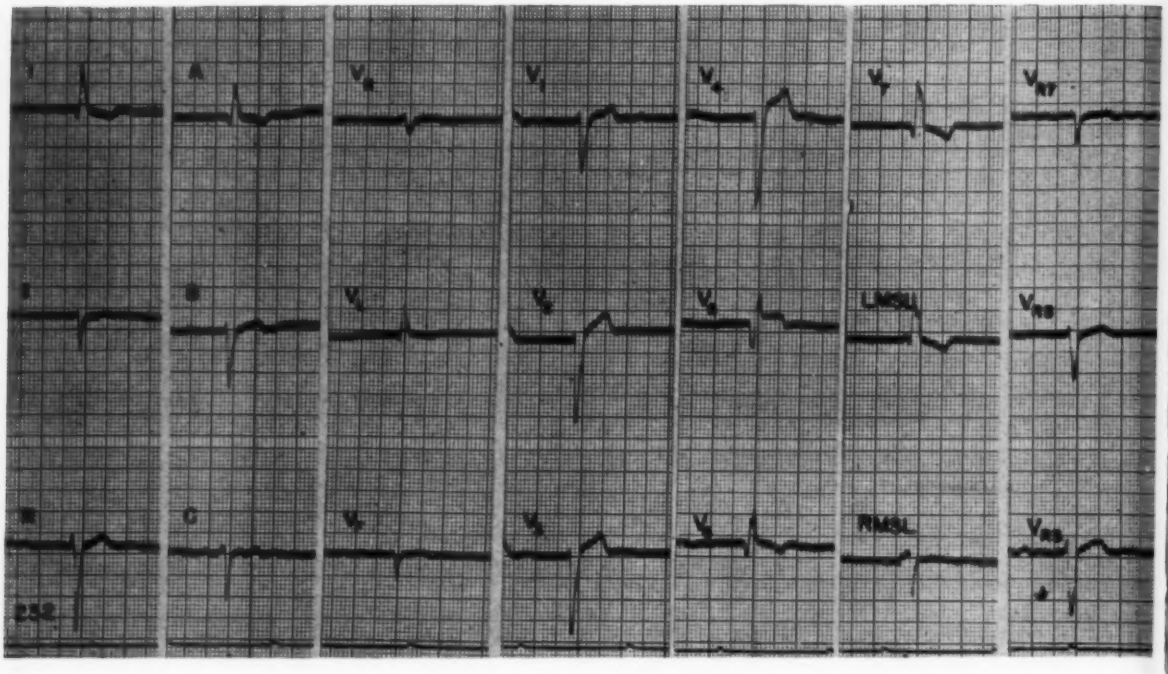

Fig. 8*A*.—Anterolateral infarction. Note the prominent Q wave in V_5 and V_6.

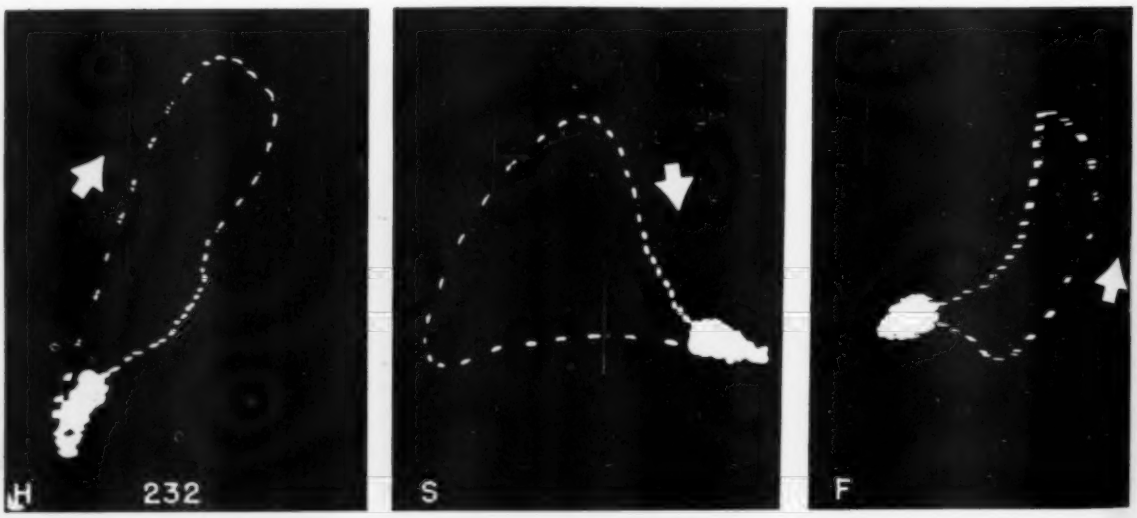

Fig. 8*B*.—Vectorcardiogram No. 232 (same case as Fig. 8*A*). The initial portion of the horizontal plane QRS sÊ loop is increased anteriorly and to the right, and the loop is inscribed in a clockwise direction. The sagittal plane loop has an initial inscription anteriorly obscured by the T loop. The frontal plane loop is inscribed in a counterclockwise direction.

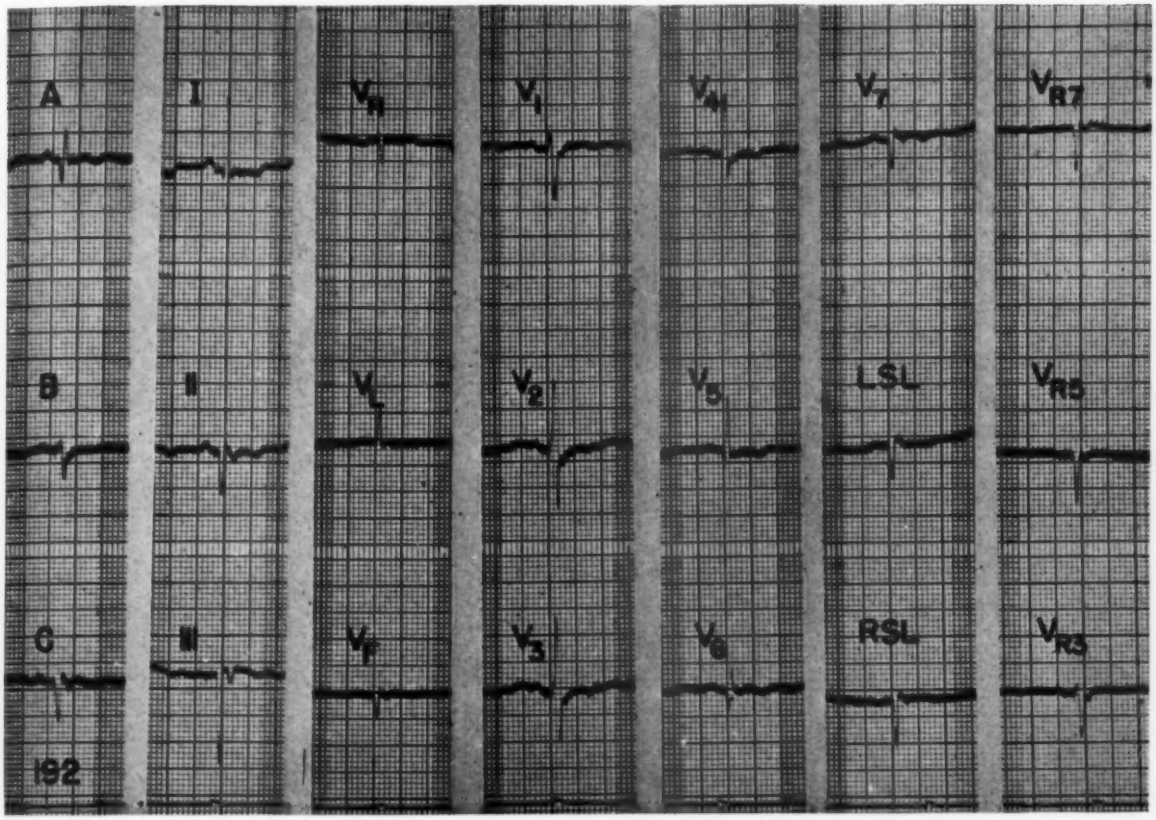

Fig. 9*A*.—Diaphragmatic and anterolateral infarction. Note the significant Q wave in II, III, V_F, and V_6.

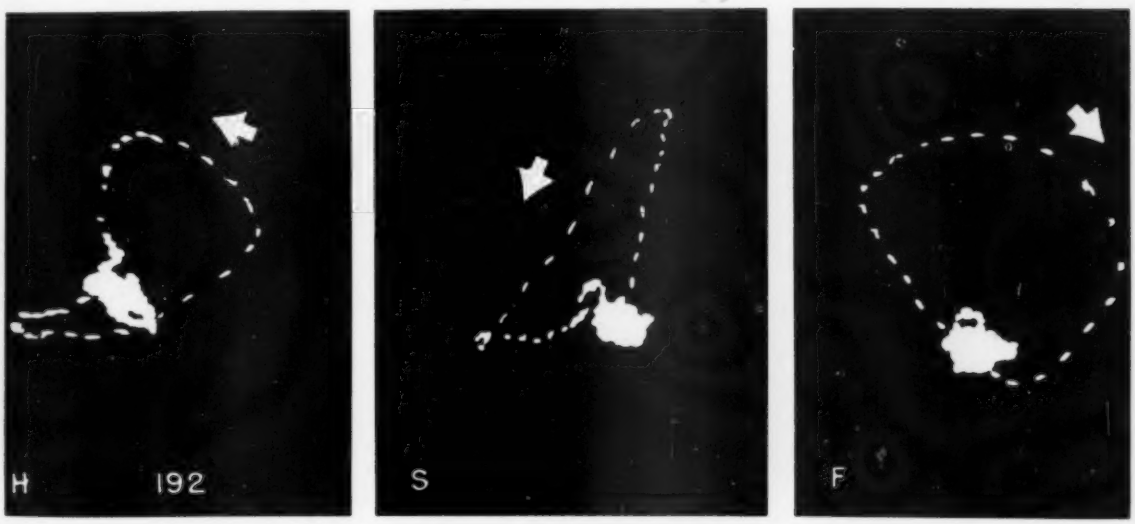

Fig. 9*B*.—Vectorcardiogram No. 192 (same case as Fig. 9*A*). The initial deflection in the horizontal plane QRS sÊ loop is increased to the right, and the sagittal plane loop is displaced upward and inscribed in a counterclockwise direction. The frontal plane loop is displaced to the right and upward.

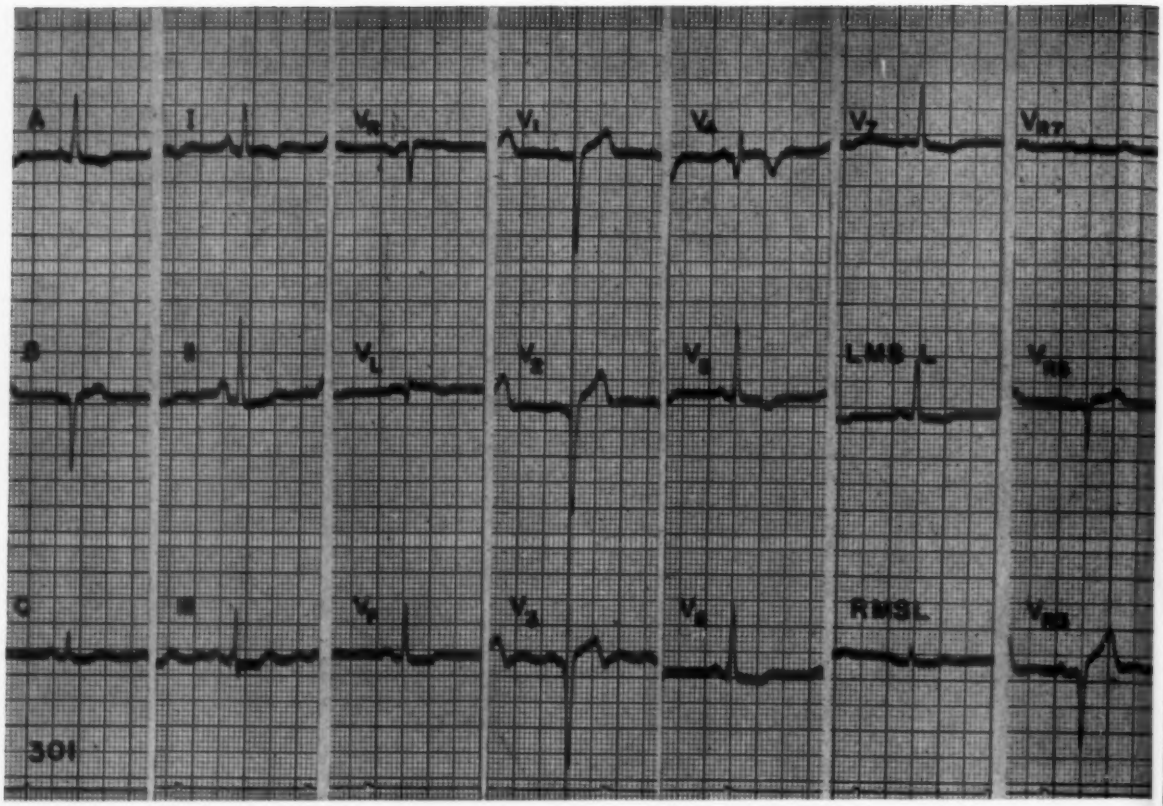

Fig. 10*A*.—Localized anterior infarction. Note the prominent Q wave in V_L and V_2 to V_4.

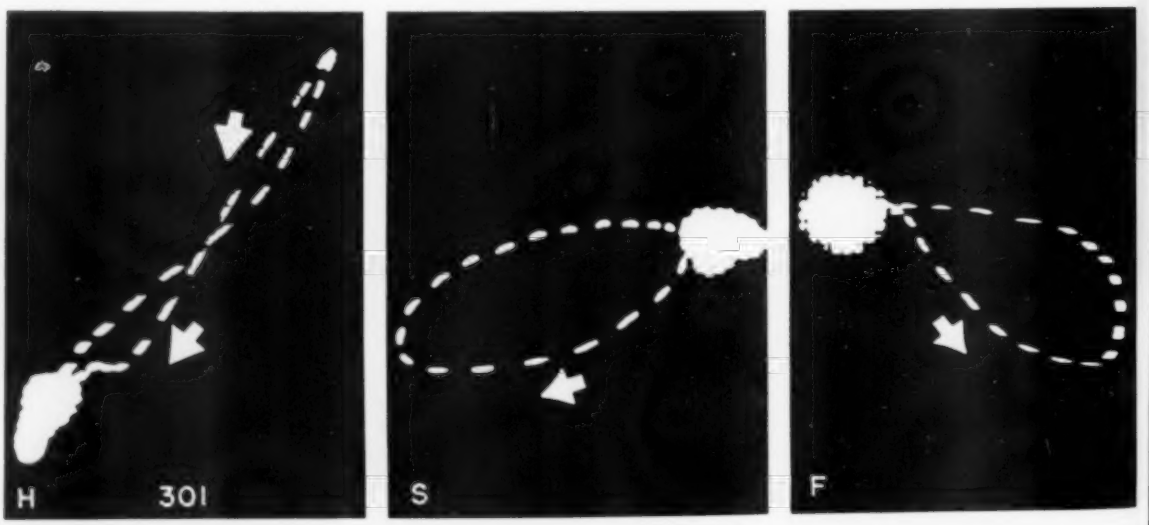

Fig. 10*B*.—Vectorcardiogram No. 301 (same case as Fig. 10*A*). The horizontal plane QRS loop is initially inscribed to the right with the distal portion inscribed in a counterclockwise direction. The sagittal and frontal plane loops are essentially unaltered.

one of the other patients, the initial deflection of the QRS sÊ loop in the horizontal plane was to the patient's right, and then it continued posteriorly in a clockwise direction to the patient's left. In the fifth patient, the QRS sÊ loop in the horizontal plane was inscribed in a counterclockwise direction, with the initial portion being to the right anteriorly followed by a concavity to the right of the centrifugal limb (Figs. 11*A* and 11*B*). The sagittal plane QRS sÊ loops were deviated posteriorly to a marked degree in all of these patients and were inscribed in a clockwise direction. The QRS sÊ loops in the frontal plane were inscribed downward

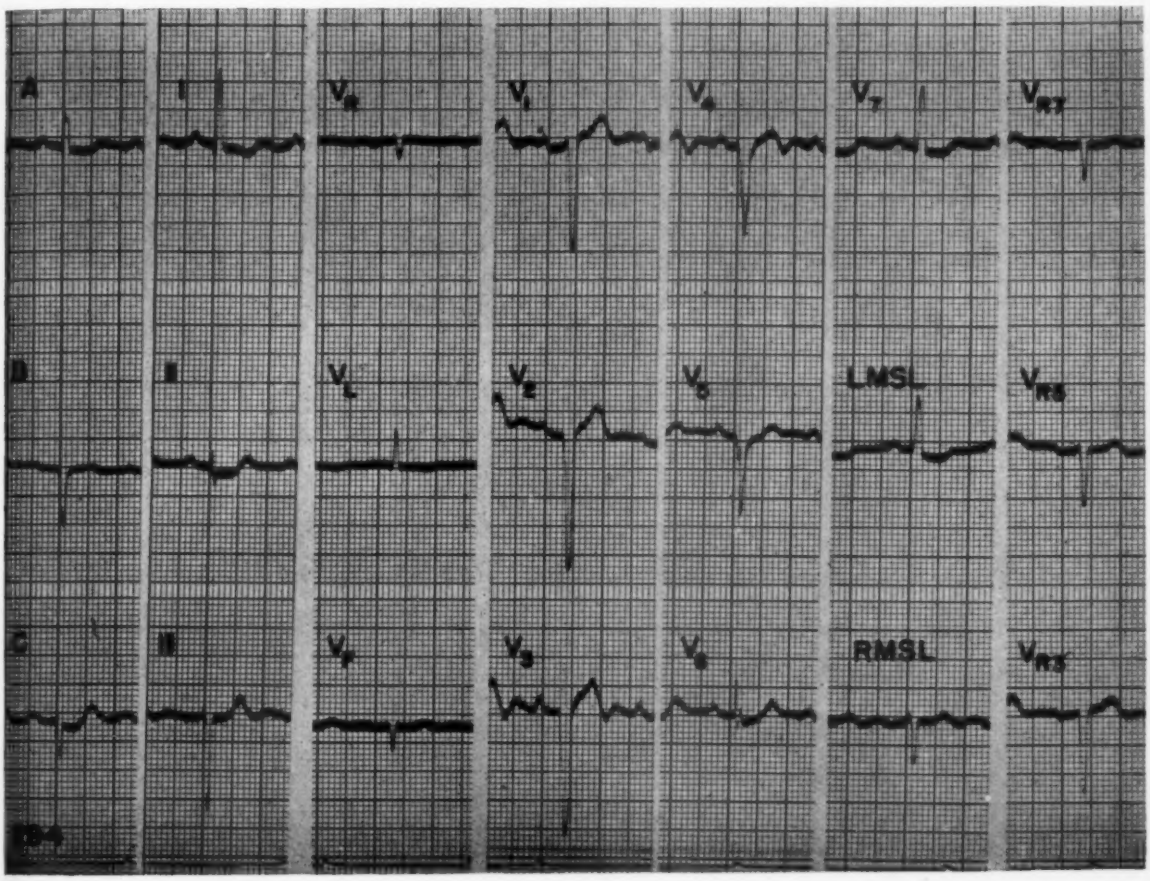

Fig. 11*A*.—Localized anterior infarction. Note the prominent Q wave in V_2 to V_5.

and to the patient's left in a counterclockwise direction. In the four instances where infarction of the inferior aspect of the heart accompanied localized infarction of the anterior aspect of the heart, each of the three varieties described before for uncomplicated localized anterior wall infarction was present in the horizontal plane. Two of the four QRS sÊ loops in this plane were inscribed in a clockwise direction (Figs. 12*A* and 12*B*).

In the sagittal plane, in all four instances, the QRS sÊ loops were deviated sharply posteriorly and were otherwise similar to those described in uncomplicated

infarction of the inferior aspect of the heart. In the frontal plane, the QRS sÊ loops were inscribed sharply upward to the patient's left and then continued in a clockwise direction.

5. *Presumptive Infarction of the Posterior Aspect of the Heart.*—In four instances of infarction of the inferior aspect of the heart and in two instances of anterolateral infarction, the QRS sÊ loops in the horizontal plane were deviated to a marked degree anteriorly (Figs. 13*A*, 13*B*, 14*A*, and 14*B*). In the sagittal plane as well, the QRS sÊ loops were deviated markedly anteriorly. Otherwise, the loops in these planes and in the frontal plane were similar to those described in uncomplicated inferior infarction or anterolateral infarction.

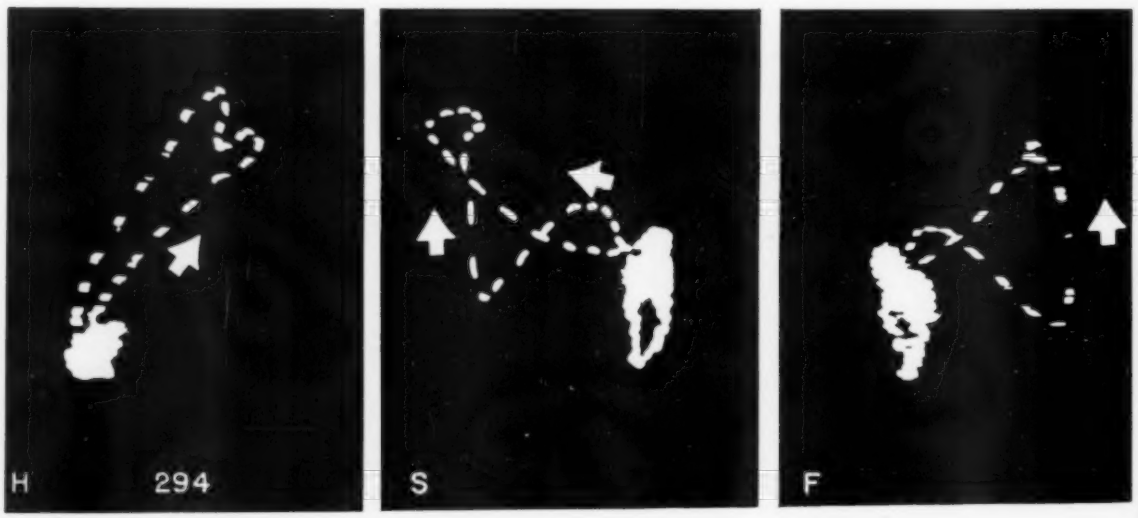

Fig. 11*B*.—Vectorcardiogram No. 294 (same case as Fig. 11*A*). The QRS sÊ loop in the horizontal plane is initially inscribed to the right and anteriorly. (The initial deflection is somewhat obscured by the T loop.) The centrifugal limb is then concave to the right. In the sagittal plane there is an initial small deflection anteriorly and downward (obscured by the T loop). The frontal plane QRS loop is initially inscribed somewhat to the right and then upward.

At the time of recording the vectorcardiograms in three other patients, there was no definite electrocardiographic evidence of infarction. However, they did have a history, typical clinical course, and serial electrocardiographic changes indicative of previous myocardial infarction.

CASE 1 (A. C).—The QRS sÊ loop in the horizontal plane was inscribed in a counterclockwise direction and was deviated anteriorly. In the sagittal plane, the loop was again deviated markedly anteriorly and inscribed in a counterclockwise direction. The QRS sÊ loop in the frontal plane was inscribed to the left in a counterclockwise direction (Figs. 15*A* and 15*B*).

CASE 2 (L. K.).—In the horizontal plane, the QRS sÊ loop was "figure 8" in configuration with the larger loop inscribed in a counterclockwise direction. The entire loop was deviated anteriorly and somewhat to the patient's right. In the sagittal plane, the loop was again deviated anteriorly and inscribed in a clockwise direction, while in the frontal plane, the QRS sÊ loop was inscribed downward and in a clockwise direction to the patient's left.

CASE 3 (E. G.).—The QRS sÊ loop in the frontal plane was deviated anteriorly and inscribed in a counterclockwise direction. The initial deflection to the right and anteriorly was much larger

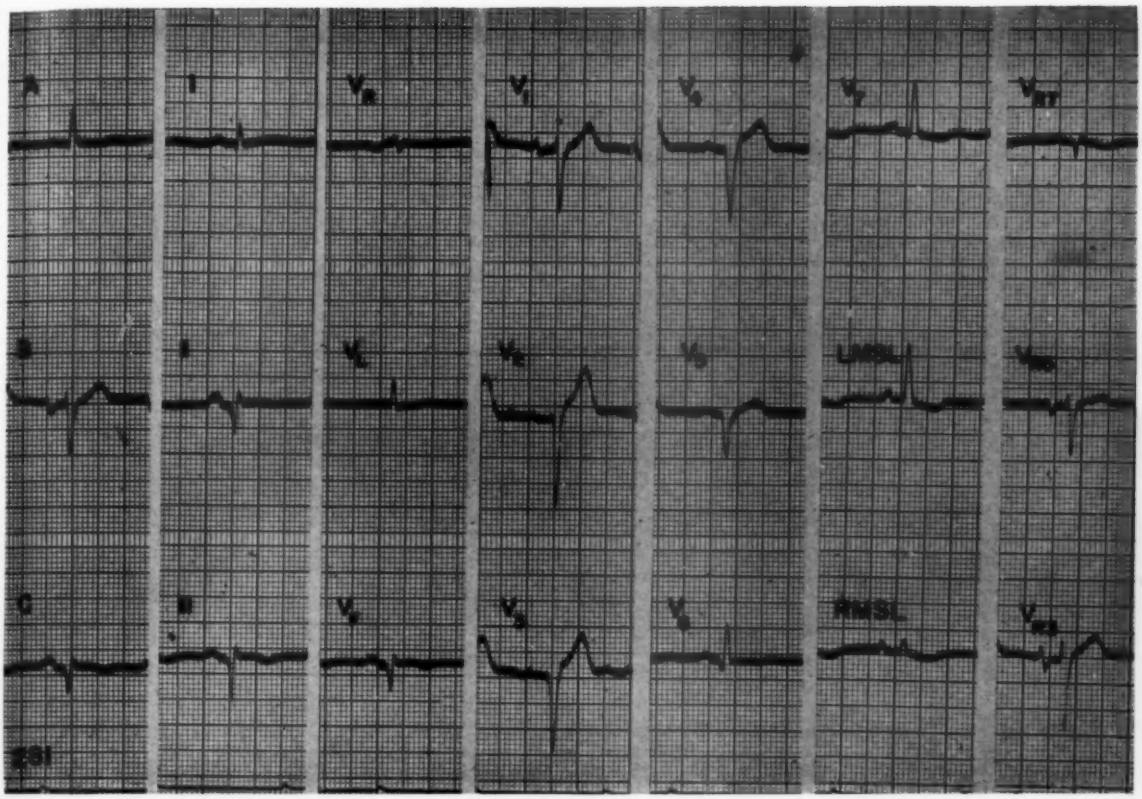

Fig. 12*A*.—Diaphragmatic and localized anterior infarction. Note the prominent Q wave in II, III, V_F, and V_3 to V_5.

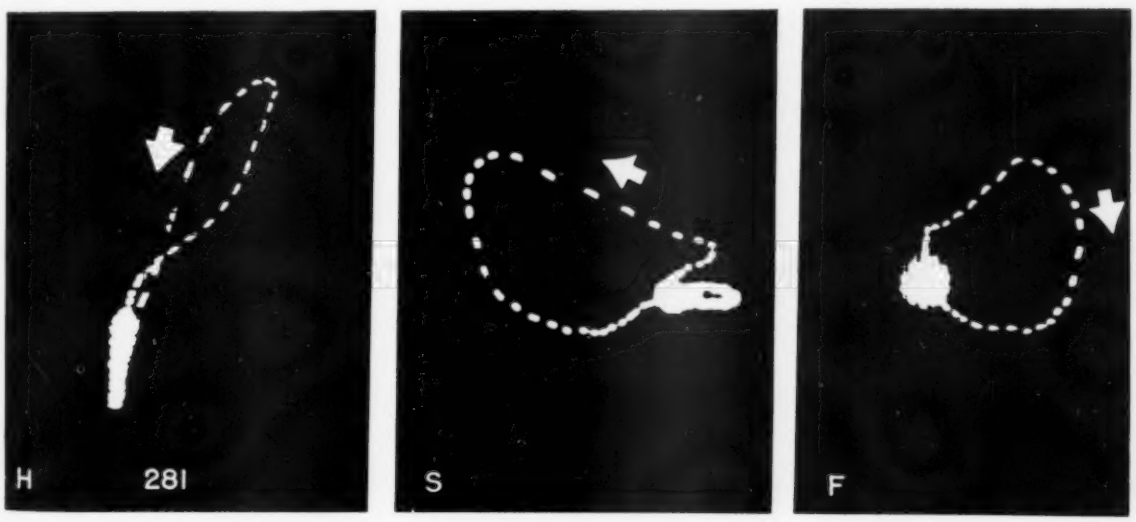

Fig. 12*B*.—Vectorcardiogram No. 281 (same case as Fig. 12*A*). The initial deflection anteriorly is somewhat obscured in the horizontal plane but is quite apparent in the sagittal plane. The QRS sÊ loop in the horizontal plane is "figure 8" in configuration. The sagittal plane loop is initially displaced upward and is inscribed in a counterclockwise direction. The initial part of the frontal plane QRS loop is also displaced upward, and the loop is inscribed in a clockwise direction.

than usual. In the sagittal plane, the QRS sÊ loop was inscribed in a clockwise direction and was deviated markedly anteriorly. The frontal plane QRS sÊ loop was "figure 8" in configuration with the initial deflection being inscribed superiorly and then to the left and downward. The distal loop was inscribed in a counterclockwise direction.

DISCUSSION

In the present study, the effect upon the orientation of the QRS sÊ loops in the horizontal, sagittal, and frontal planes corresponded to the location of the infarct as revealed by the routine electrocardiogram.

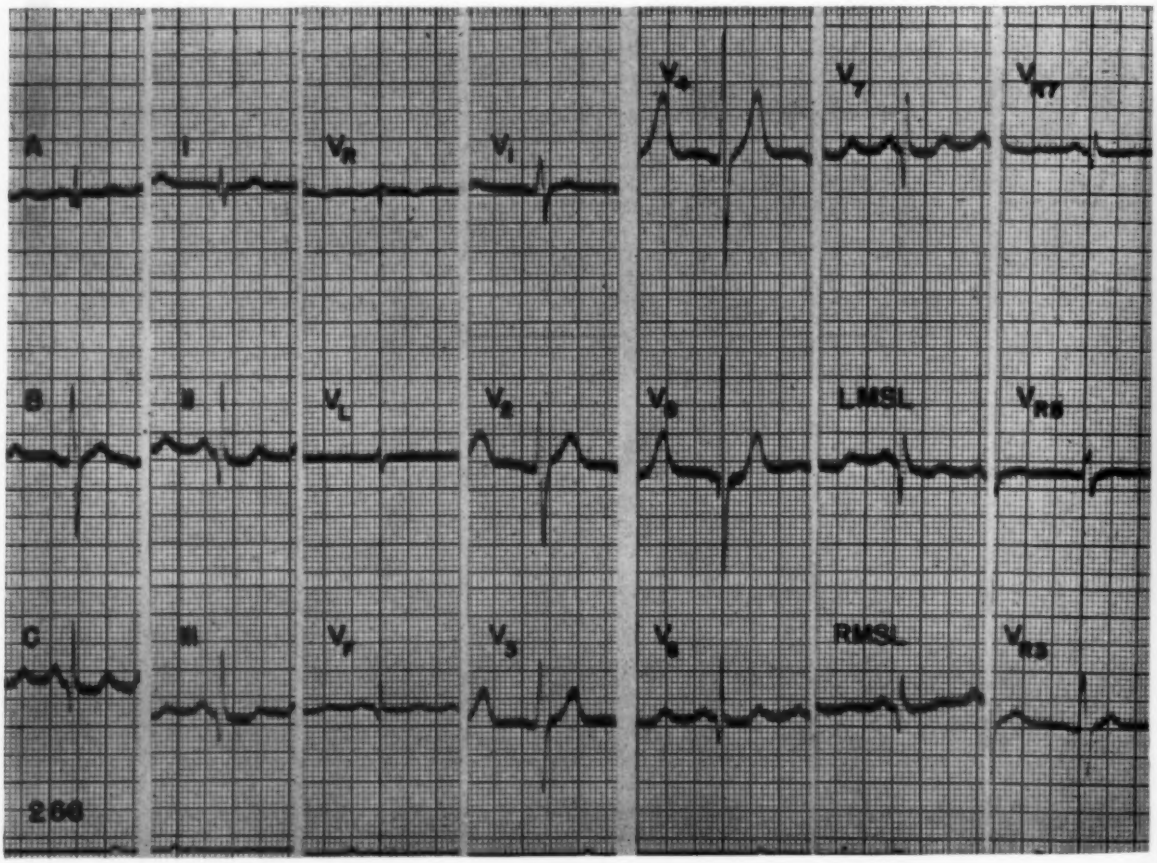

Fig. 13*A*.—Posterior and diaphragmatic infarction. Note the prominent Q waves in II, III, V_F, and V_6 and the RS configuration of V_{R5}, V_{R2}, and V_1 to V_4.

1. *Horizontal Plane.*—The normal QRS sÊ loop in the horizontal plane is characterized by an initial small deflection anteriorly, usually to the patient's right, followed by the smooth inscription of the loop in a counterclockwise direction to the left and posteriorly. The initial deviation is recorded in right precordial leads as a small R wave and in left precordial leads as a small Q wave. The inscription of the loop to the left is correlated with the recording of S waves over the right precordium and R waves over the left. When the instantaneous vector approaches the recording electrode, the R wave is written.

Infarction involving predominantly the anterior portion of the heart will result in the production of a new vectorial force directed posteriorly and essentially perpendicular to the electrically inert area. Hence, in the present study, anteroseptal infarction resulted in the loss of the initial deflection anteriorly and to the right in the inscription of the loop, the loop now being inscribed sharply posteriorly. Localized anterior wall infarction usually left the septal deflection unaltered, but the loop was deviated posteriorly and to the right, being at times inscribed in a clockwise direction rather than counterclockwise. In a few instances, the loop was "figure 8" in configuration. In infarction of the lateral wall, the QRS sÊ loop was deviated markedly to the right and posteriorly with the septal deflection again remaining unaltered.

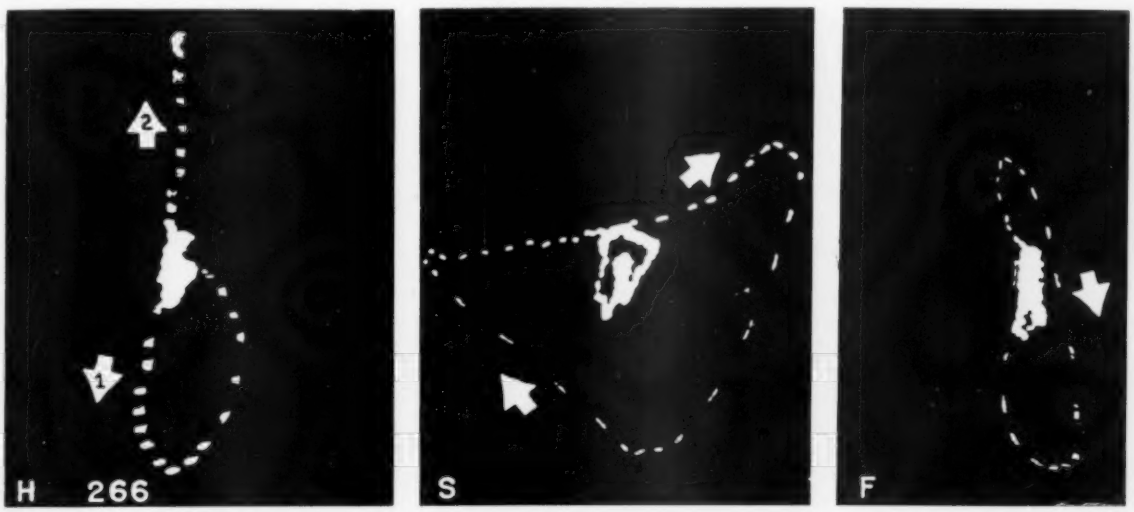

Fig. 13*B*.—Vectorcardiogram No. 266 (same case as Fig. 13*A*). The initial portion of the horizontal plane QRS sÊ loop is deviated anteriorly. The entire loop is deviated to the right. The sagittal plane QRS loop is initially displaced anteriorly and upward. The frontal plane QRS loop is inscribed in a clockwise direction and initially displaced upward.

The alteration in the direction of inscription of the QRS sÊ loop from counterclockwise to clockwise in the horizontal plane would seem to indicate that the electrically functional myocardium now lies more posterior than normal, because of the loss of electromotive forces formerly contributed by the now electrically inert infarcted area. There is, thus, augmentation of the electromotive forces arising from the diametrically opposite area with the QRS sÊ loop being displaced in the direction of the electrically active tissue. In left bundle branch block, the horizontal plane QRS sÊ loop is also inscribed in a clockwise direction. Unlike the instances of infarction, the interrupted segments of the loop are extremely close together in left bundle branch block, offering evidence of conduction delay.[11]

The terminology used in this report for the localization of infarction was adopted in order to distinguish more clearly between the electrocardiographic effects of various infarctions. Hence, inferior infarction is used synonomously with diaphragmatic infarction. Separated from this group is the category of

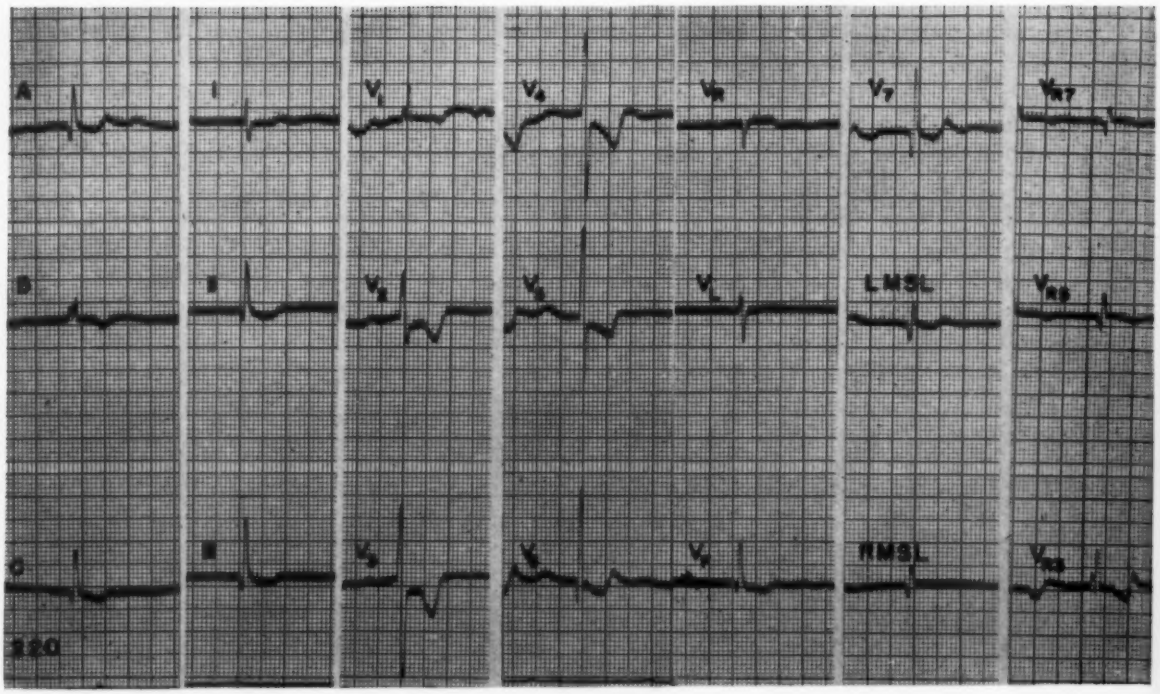

Fig. 14*A*.—Posterior and lateral infarction. Note the prominent Q wave in V_6 and V_7 and the prominent R wave in V_{R3} and V_1 to V_5.

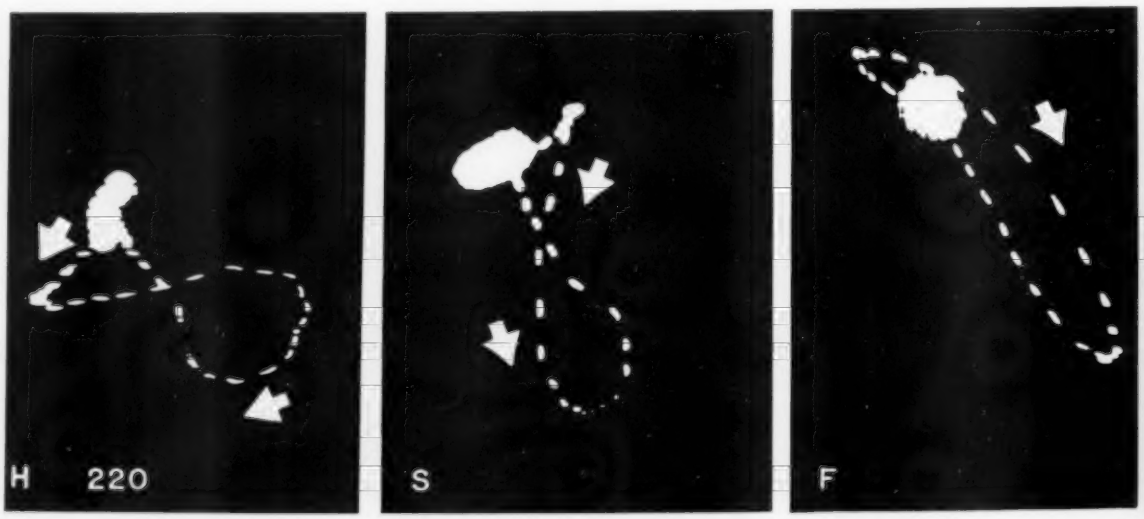

Fig. 14*B*.—Vectorcardiogram No. 220 (same case as Fig. 14*A*). Entire QRS sÊ loops in the horizontal and sagittal planes are displaced markedly anteriorly. The initial deflections in the horizontal and frontal planes are to the right.

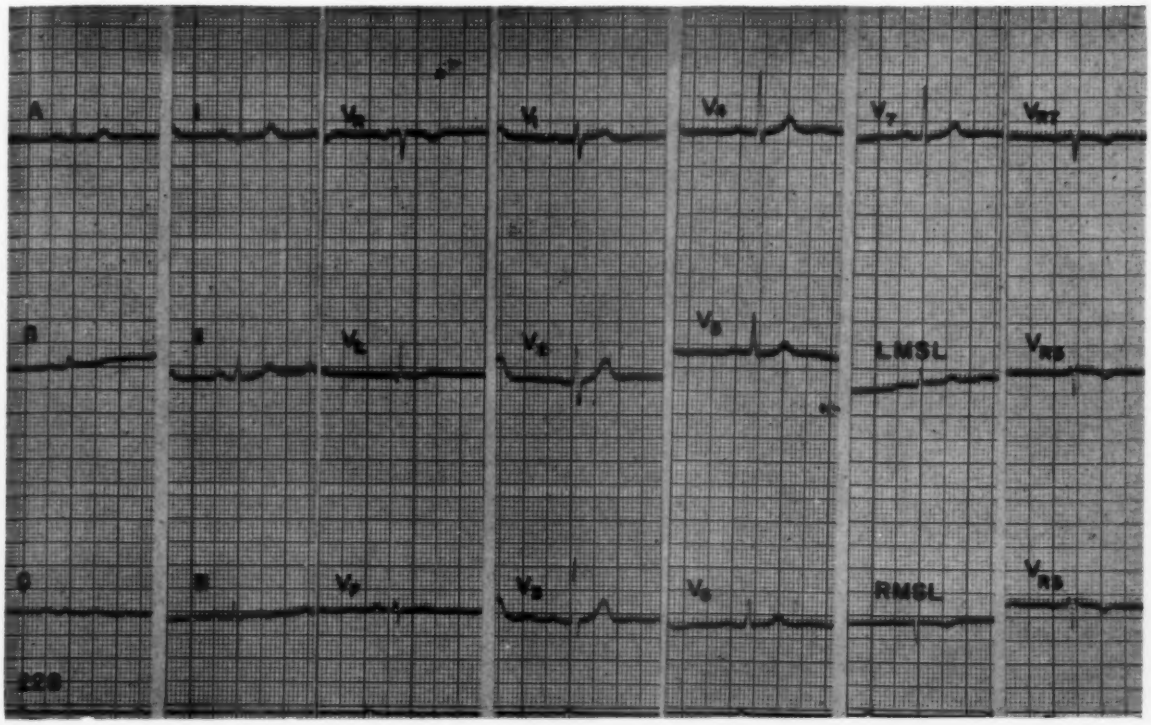

Fig. 15*A*.—Posterior infarction. Note the absence of a prominent Q wave in any lead;

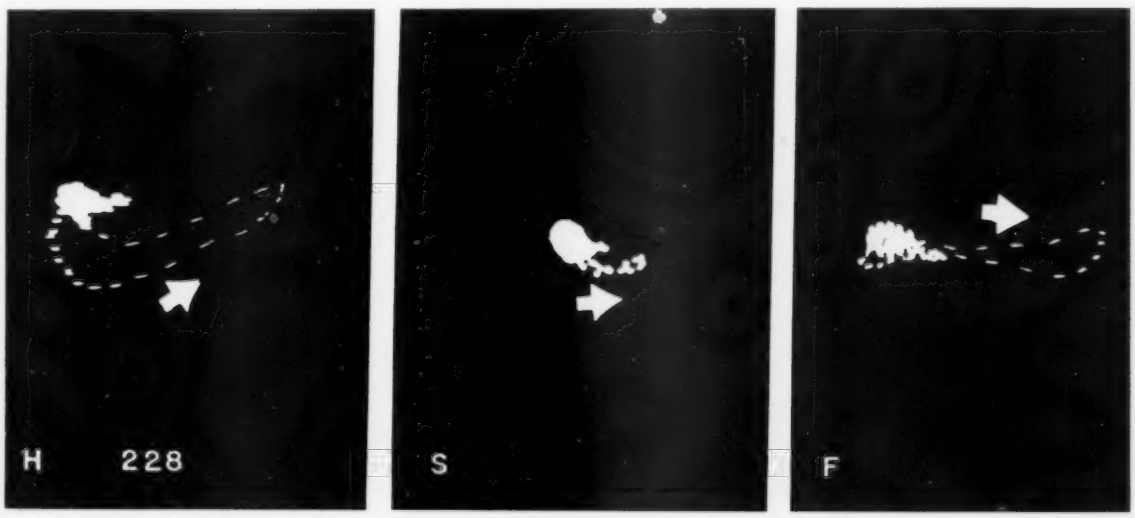

Fig. 15*B*.—Vectorcardiogram No. 228 (same case as Fig. 15*A*). The QRS sÊ loops in the horizontal and sagittal planes are displaced markedly anteriorly. The frontal plane QRS loop is "figure 8" in configuration.

posterior infarctions. The latter group probably includes infarction of the infra-atrial portion of the left ventricle rather than the diaphragmatic surface.

In infarction of the posterior aspect of the heart, the horizontal plane QRS sÊ loop should be expected to occupy a more anterior position than normal, and such loops were obtained in several of the patients included in the present report.

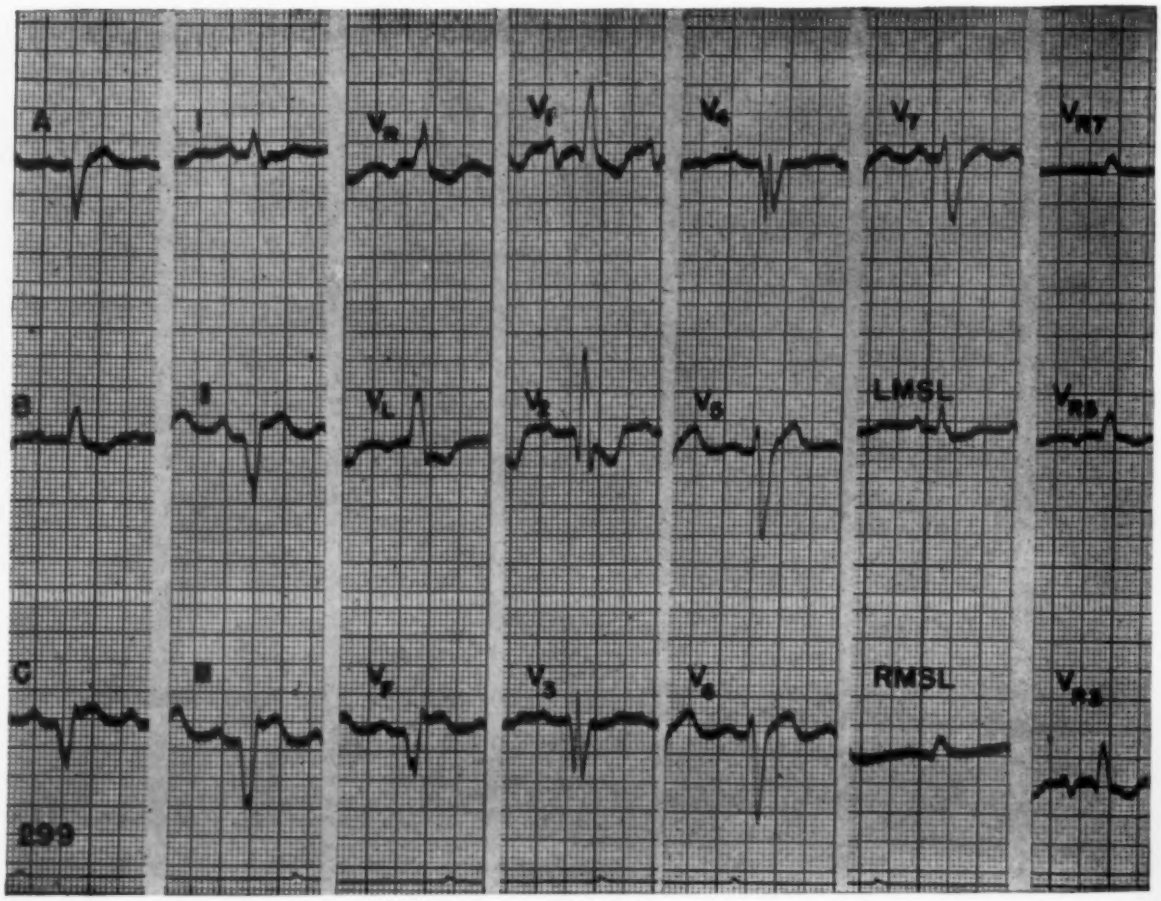

Fig. 16*A*.—Diaphragmatic and anterior infarction. Note the prominent Q wave in V_F and V_4, and the prominent R wave in V_{R7}, V_{R5}, V_{R3}, V_1, and V_R.

Of all infarctions, the most difficult to diagnose are those localized to the infra-atrial margin, or posterior aspect of the heart. The abnormal resultant vector due to posterior infarction is directed anteriorly and essentially perpendicular to the frontal plane and is therefore usually not reflected in routine electrocardiographic records. Esophageal leads are of little help in this regard because of the variability of the transition zone and the frequency with which normal patients may have prominent Q waves registered at isolated esophageal levels.[12,13] It is important to note that in some instances marked anterior displacement of the QRS sÊ loops may well indicate posterior wall infarction. Nine patients in the present study had marked anterior displacement of the QRS sÊ loops. Such

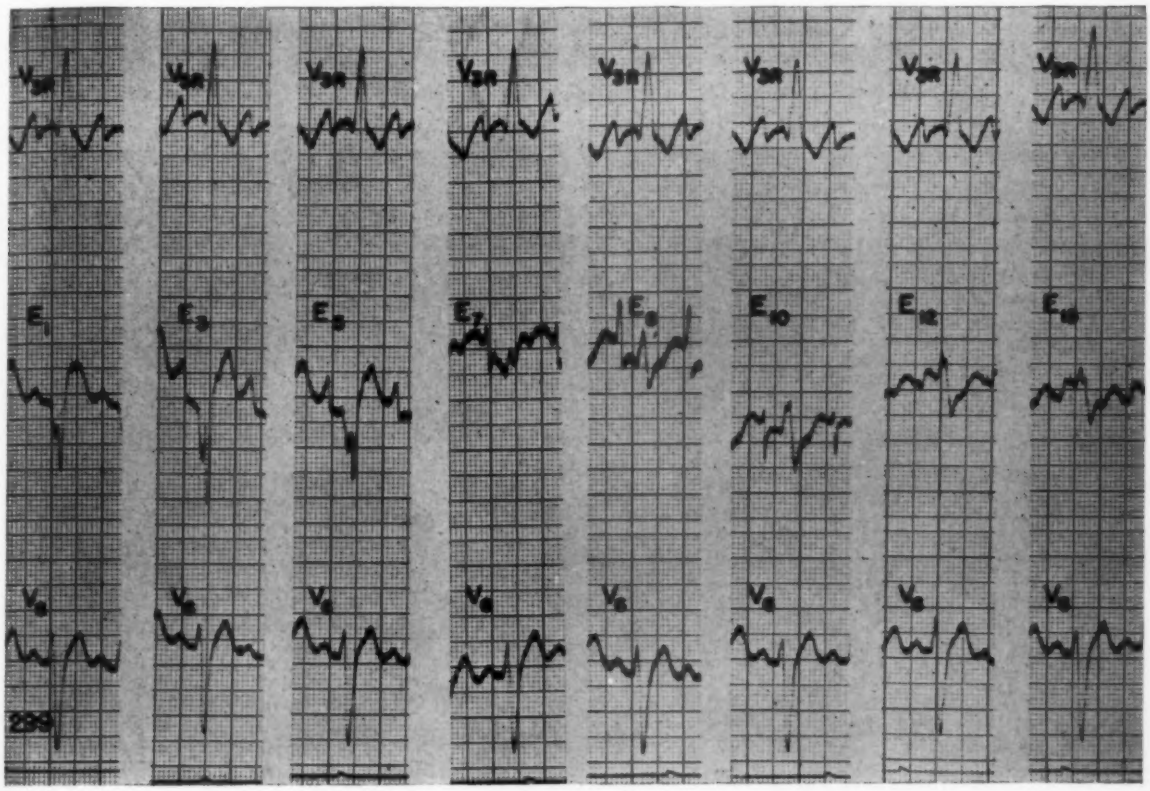

Fig. 16*B*.—Esophageal electrocardiogram (same case as Fig. 16*A*). Note the prominent Q wave in E_1 and the prominent R wave in E_8 to E_{15}. An atrial intrinsic deflection is recorded in E_3 to E_{10}.

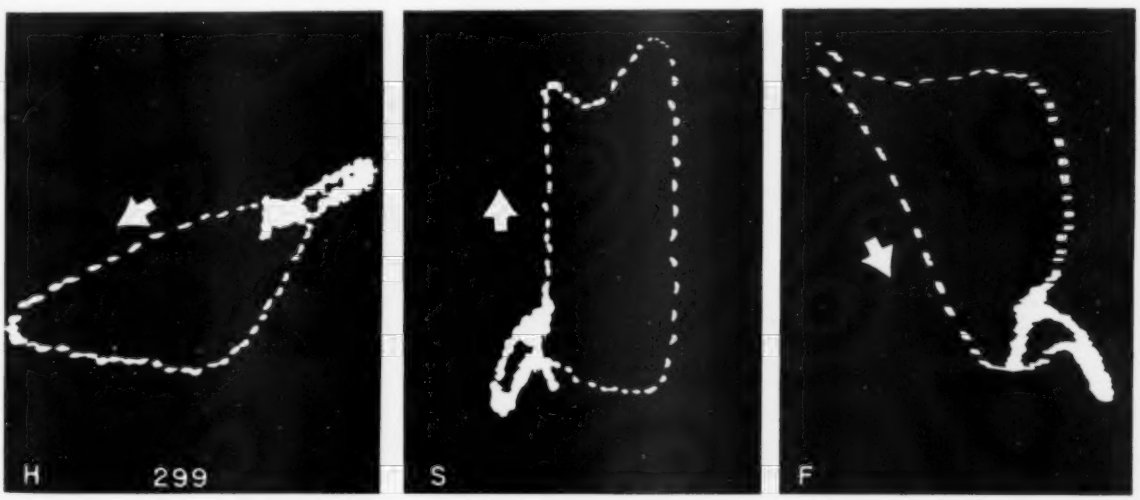

Fig. 16*C*.—Vectorcardiogram No. 299 (same case as Figs. 16*A* and 16*B*). The entire QRS sÊ loop in the horizontal plane is displaced to the right and anteriorly. The QRS sÊ loop in the sagittal plane is displaced markedly superiorly and anteriorly. The frontal plane QRS loop is displaced to the right and superiorly.

displacement is strongly suggestive of the loss of electromotive forces contributed by the posterior part of the heart as in infarction.

The initial anterior deviation of the QRS sÊ loop in posterior infarction may be ascribed to unbalanced forces of the anterior portion of the interventricular septum because of the synergism of the normal septal forces and the abnormal vector of the posterior septal infarction.

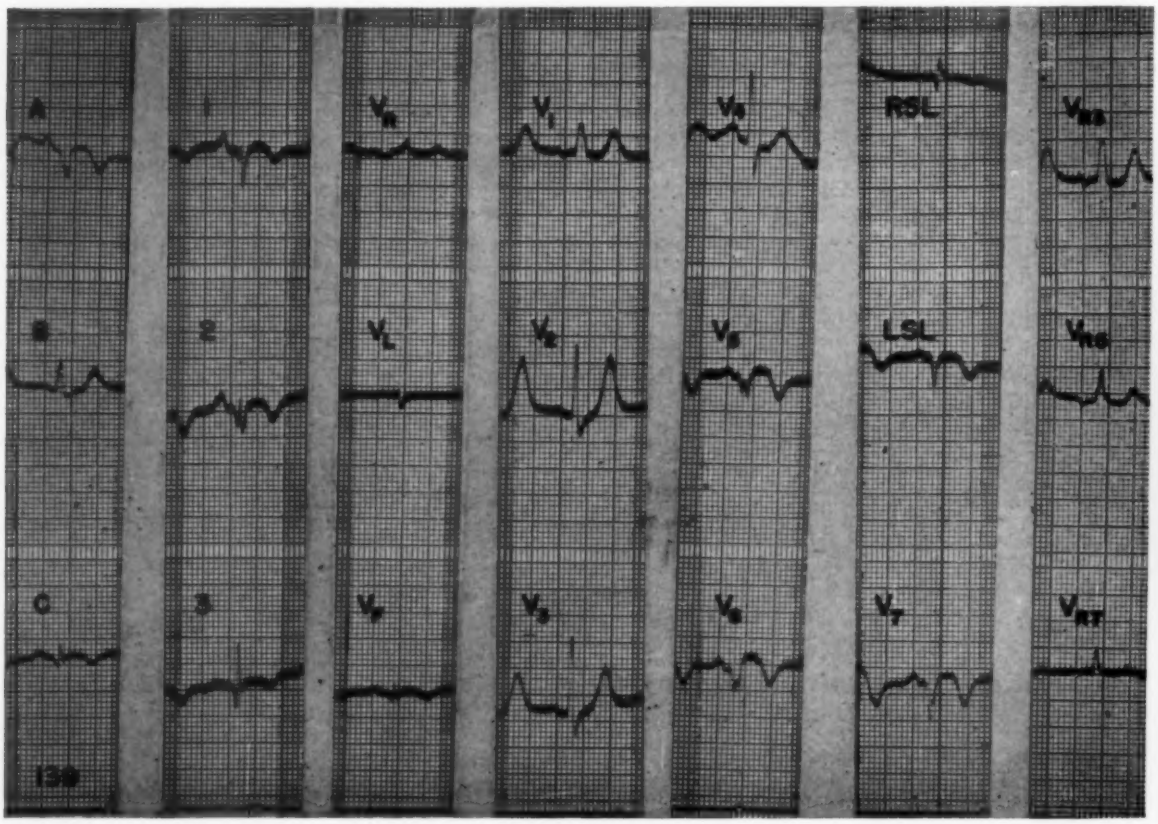

Fig. 17*A*.—Anterolateral and diaphragmatic infarction. Note the prominent Q wave in I, II, III, V_F, V_5, and V_6 and the prominent R wave in V_R, V_{R3}, V_{R5}, V_{R7}, and V_1 to V_3.

The horizontal plane QRS sÊ loops were displaced to the right and anteriorly in eight patients in whom prominent R waves were recorded over the right precordium and QS waves over the left (Figs. 16*A*, 16*B*, 16*C*, 17*A*, 17*B*, 18*A*, and 18*B*). The reorientation of the electromotive forces in these instances can be ascribed to the loss of electromotive forces over the left, laterally and posteriorly, so that the forces over the right anteriorly are now augmented. The registration of tall R waves over the right precordium thus occurs since the electromotive forces of the functional myocardium on the right anteriorly are now greater than the left laterally and posteriorly. The electrocardiograms of twelve similar cases have recently been reported in association with inferior, inferolateral, or anterolateral infarction.[14]

The registration of Q waves over the precordium indicates that the balance of forces is such that the instantaneous electrical axis projects upon the negative side of the axis of the recording electrode so that the electromotive forces are directed away from the electrode. Hence, in infarction of the anterior or lateral aspect of the heart, the recording of a prominent Q wave over the precordium indicates that the new resultant instantaneous electrical axis projects upon the negative side of the axis of the recording electrode. Multiple precordial leads thus permit the exploration of the precordium to determine the orientation of this new abnormal vector.

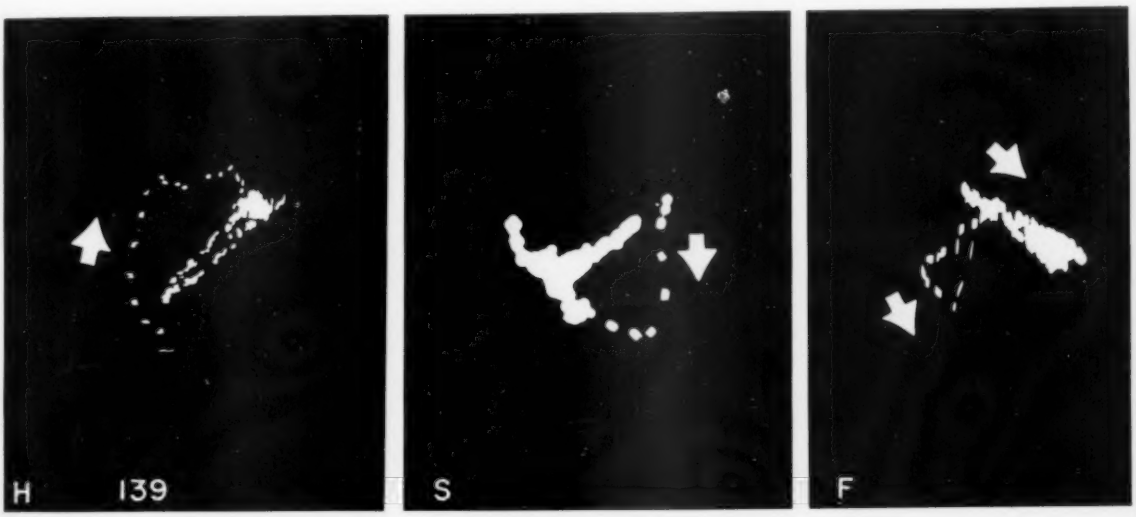

Fig. 17*B*.—Vectorcardiogram No. 139 (same case as Fig. 17*A*). The entire loop in the horizontal plane is displaced to the right and anteriorly and is inscribed in a clockwise direction. The sagittal plane loop is deviated anteriorly and upward, and the frontal plane loop is deviated to the right and upward.

2. *Sagittal Plane.*—The normal QRS sÊ loop in the sagittal plane is usually characterized by an initial, small deflection anteriorly, with the loop then being inscribed downward, posteriorly, and in a clockwise direction. The inscription anteriorly is usually correlated with the recording of a small R wave over V_1 and V_2. Leads V_F and E_1 (recorded at subdiaphragmatic levels) are essentially similar. The QRS deflections are initially positive or negative depending upon whether the instantaneous vector points to or away from these leads, with the magnitude of the deflection depending upon the magnitude of the projection. A similar analysis can be made of the complete esophageal patterns.

When the infarcted areas in the present study were localized to the inferior or diaphragmatic aspect of the heart, the sagittal plane QRS sÊ loop was shifted upward in a superior direction. The initial deflection anteriorly usually continued upward so that the entire loop was inscribed in a counterclockwise direction. The loops, in other instances, were inscribed in a clockwise direction after the registration of a much larger than normal initial deflection upward. In every instance, the upward deviation of the initial deflection was accompanied

by the registration of prominent Q waves in V_F and in lower esophageal leads. Whereas, at supracardiac levels, the esophageal leads normally record an essentially downward or negative deflection, the QRS complex may be essentially positive in infarction of the inferior or diaphragmatic aspect of the heart. The new orientation of the QRS sÊ loop in such instances can be ascribed to the production of a new resultant vectorial force because of the electrically inert areas of infarction located inferiorly and the augmentation of forces in the diametrically opposite direction, i.e., upward.

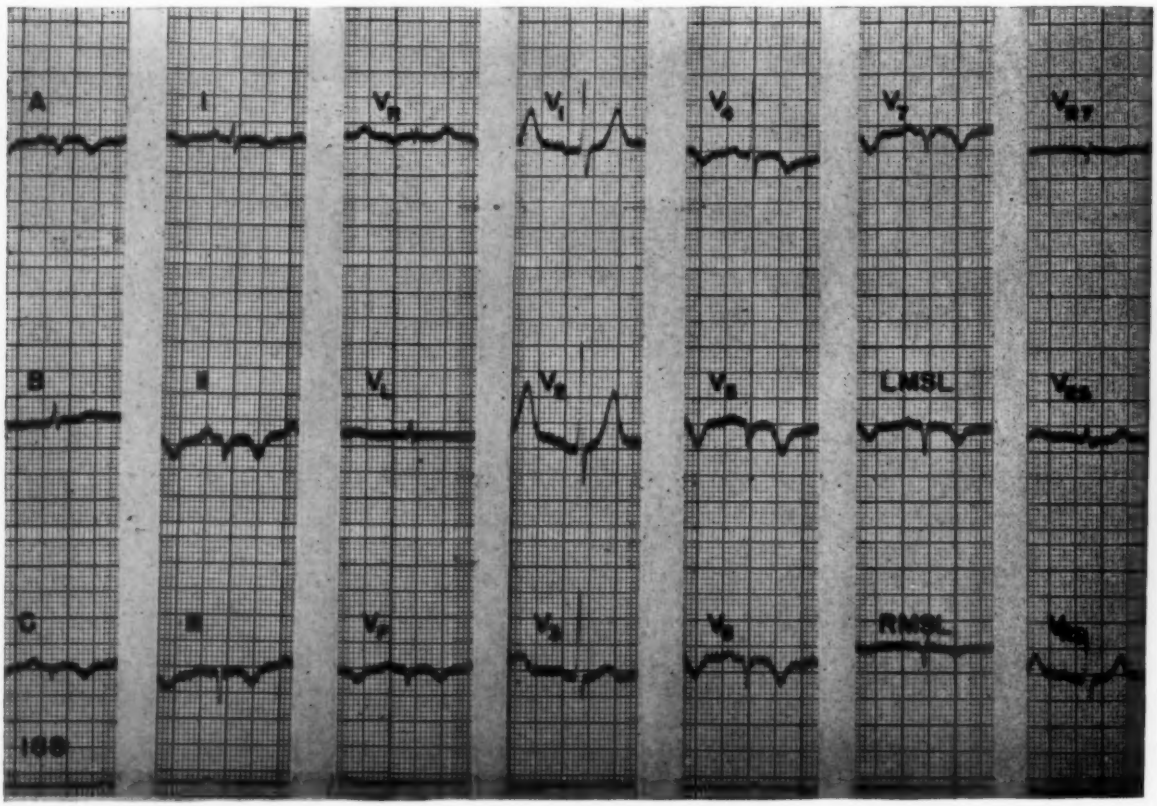

Fig. 18*A*.—Anterolateral and diaphragmatic infarction. Note the prominent Q wave in II, III, V_F, V_5, and V_6 and the prominent R waves in V_R, V_{R5}, V_{R3}, and V_1 to V_4.

The QRS sÊ loop in the sagittal plane was deviated markedly anteriorly in several instances as already described. Posterior deviation of the QRS sÊ loop in the sagittal plane occasionally occurred in the present study when anteroseptal or anterior wall infarction occurred. This deviation may be ascribed to loss of the electromotive forces from that portion of the anterior wall or septum normally exerting an influence on the sagittal plane.

3. *Frontal Plane.*—The QRS sÊ loop in the frontal plane has been subject to most study, since it is this loop which can be readily derived from the standard extremity leads. In the frontal plane the direction of the inscription of the nor-

mal QRS sÊ loop may be in a clockwise or counterclockwise direction. When there is no axis deviation or a tendency to right axis deviation, the loop is inscribed downward and somewhat to the patient's left in a clockwise direction (Fig. 2). When there is a tendency to left axis deviation, the loop is inscribed downward and still more to the patient's left and usually in a counterclockwise direction. Although the Einthoven method of registration of component leads was not utilized in the present study, good correlation was usually obtained with the standard leads. An infarction localized to the inferior or diaphragmatic aspect of the heart was accompanied by an initial inscription of the QRS sÊ loop upward and usually to the left in a clockwise direction. This was accompanied by the inscription of a prominent Q wave in Leads III and V_F since the projection of the instantaneous electrical axis was on the negative side of these leads.

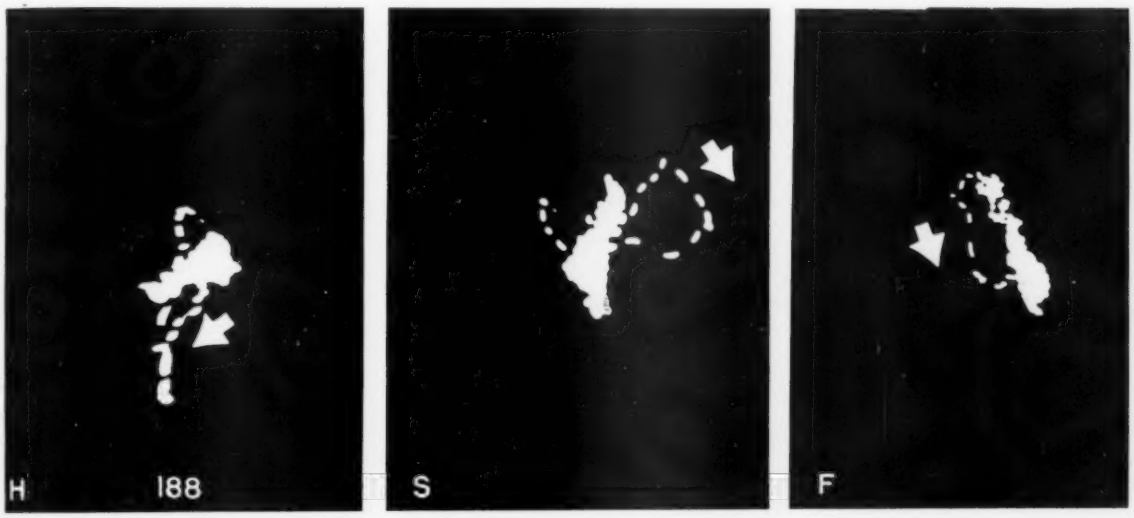

Fig. 18*B*.—Vectorcardiogram No. 188 (same case as Fig. 18*A*). The QRS sÊ loop in the horizontal plane is deviated to the right and anteriorly. The sagittal plane loop is displaced upward and anteriorly, and the frontal plane loop is displaced to the right and superiorly.

Lateral or extensive anterior wall infarctions were accompanied by the inscription of the QRS sÊ loop to the patient's right, which was correlated with the initial negative deflection or Q wave in Lead I. Localized anterior or posterior infarctions (as distinguished from inferior or diaphragmatic) exerted no influence on this plane since in such instances the new vectorial force is essentially perpendicular to the frontal plane.

In no patient was there any evidence of conduction delay such as would be manifested by the close grouping together of interrupted segments of the QRS sÊ loop.[11]

In the present study, in ten instances a prominent R wave was recorded in V_R in association with myocardial infarction (Figs. 5*A*, 5*B*, 19*A*, and 19*B*). Some investigators have attributed such a finding to anatomical rotation of the heart so that the potentials of the posterobasal portion of the left ventricle are transmitted to the right arm.[15,16] It is more likely that a reorientation of the

resultant electromotive forces rather than anatomical reorientation plays a major role. In the present study, in every instance of infarction in which a prominent R wave was registered in V_R, there was electrocardiographic evidence of infarction of the lateral-apical portion of the left ventricle, usually with some inferior or anterior involvement in addition. In these instances, the new and abnormal spatial vector was directed superiorly, to the right, and often posteriorly, as evidenced by the increased positivity in the right arm. There

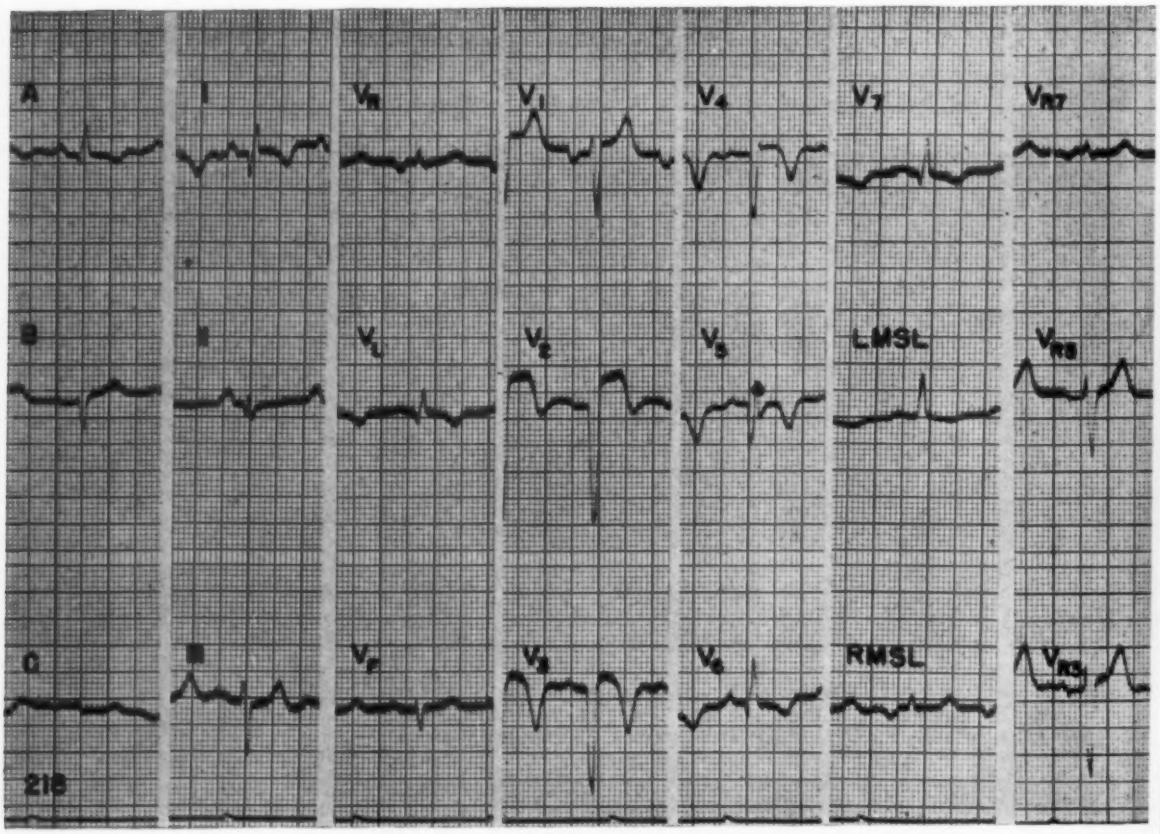

Fig. 19*A*.—Anterior infarction. Note the prominent Q wave in V_L and V_2 to V_6 and the prominent R wave in V_R.

was no conduction delay manifested in the QRS sÊ loops in these patients. The association of right axis deviation with myocardial infarction has been noted by earlier investigators.[17] A prominent R wave in V_R in association with two instances of inferolateral infarction was recently reported.[14] The upright deflection was ascribed to the absence of opposing electrical effects.

The QRS sÊ loop as recorded by the cathode ray oscillograph represents the advancement of the terminus of an instantaneous vector during the time consumed by the spread of the wave of accession. This vector at any one instant is the resultant of many diverse electromotive forces which vary in direction and

magnitude.[1,2,3] The orientation of the normal QRS sÊ loop downward, posteriorly, and to the left can be attributed to the generation of electromotive forces of greater magnitude by the left ventricle as compared to the right, particularly by the lateral and posterior wall of the left ventricle.

The record of the electromotive forces at any one particular region is influenced by the electromotive forces arising in that area and also by forces arising in distal areas, especially those which are diametrically opposite. Hence, the loss of electromotive forces due to destruction of tissue with resultant electrically inert areas will not only alter profoundly the electrocardiogram recorded over that area,[1,2,3] but will also affect the pattern recorded distally, particularly that recorded directly opposite the inert area. The value of multiple precordial leads thus lies in determining the abnormal resultant vector.

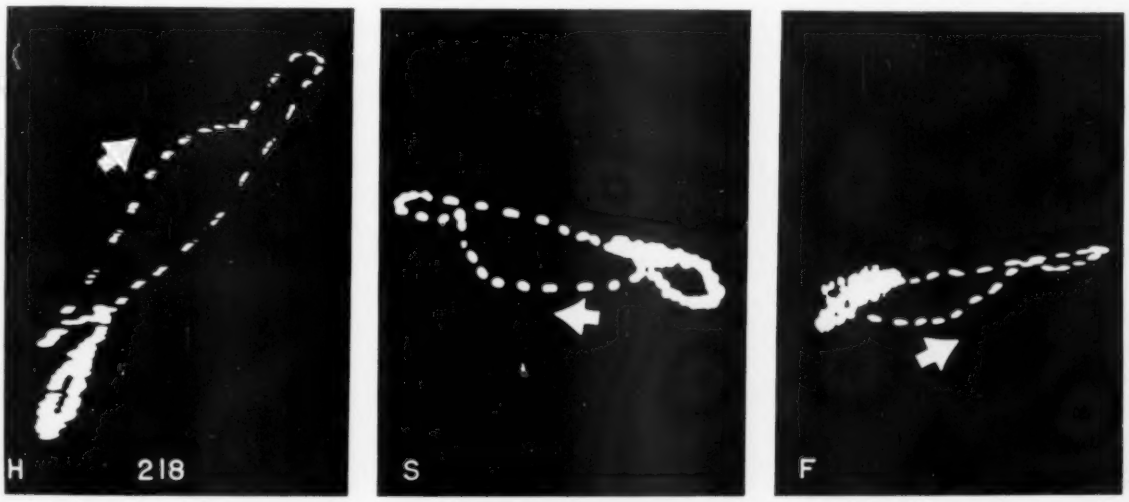

Fig. 19*B*.—Vectorcardiogram No. 218 (same case as Fig. 19*A*). The initial deflection to the right in the horizontal plane QRS sÊ loop is increased, and the loop is inscribed in a clockwise direction. The sagittal plane loop is displaced somewhat posteriorly. The initial deflection in the frontal plane loop is to the right, and the loop is inscribed in a counterclockwise direction.

The new resultant electromotive forces in infarction are therefore due to the existence of a new analytic area which augments the electromotive forces of the diametrically opposite area because of the now unopposed potential in the uninvolved region.[1] Hence, infarction involving predominantly the lateral wall or apex will cause loss of the electromotive forces normally arising from that area and will augment the electromotive forces directed in the opposite direction. The new and abnormal spatial vector will therefore be directed superiorly and often posteriorly to the right.

Infarction of the anterior wall will likewise augment the electromotive forces directed in the opposite direction. The new and abnormal spatial vector in this instance will be directed posteriorly and to the right. Infarction of the inferior or diaphragmatic aspect of the heart will thus augment the electromotive forces directed superiorly, while infarction of the posterior aspect will augment the electromotive forces directed anteriorly.

Since one infarcted area by its loss of electromotive forces causes a new resultant vectorial force, more than one infarcted area in the same heart will also produce a new resultant vector force, the direction and magnitude of which will depend upon the spatial orientation of the electrically inert areas. Hence, an infarction of both the anterior and posterior walls may theoretically show no appreciable displacement of the QRS sÊ loop. An infarction of the anterior,

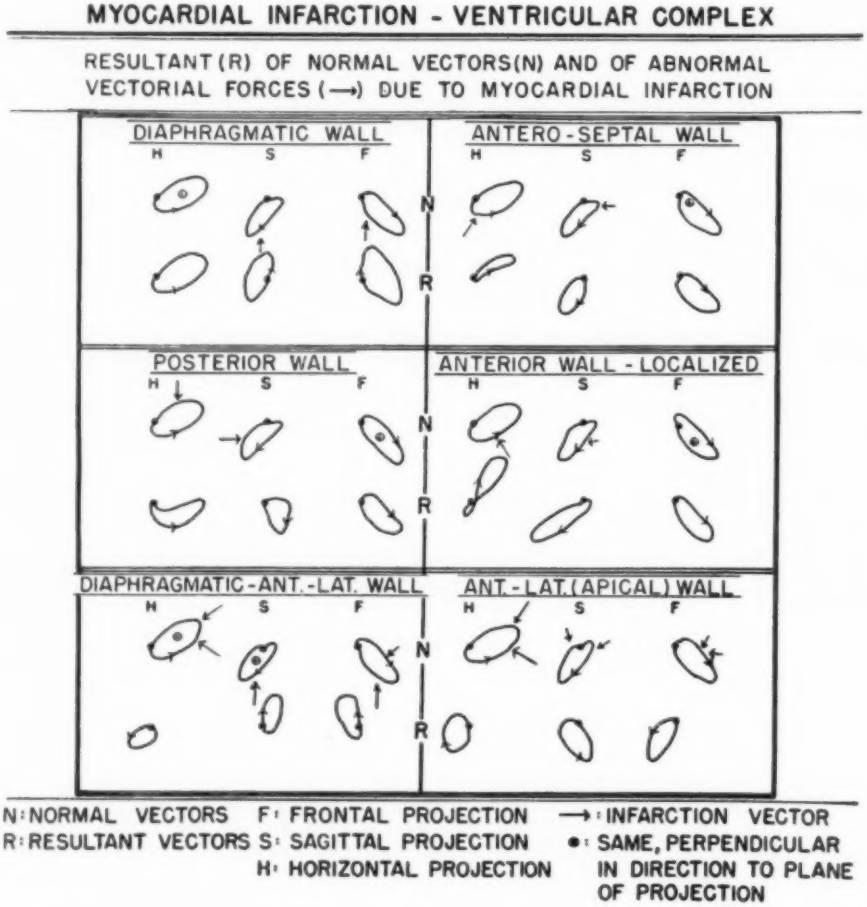

Fig. 20.— Schematic representation of the spatial projections of the vectorcardiograms in the horizontal, sagittal, and frontal planes. The resultant vectorcardiograms following various localizations of myocardial infarction are shown with the arrows indicating the direction in which the abnormal vectorial force displaces the QRS sÊ loop in each plane.

posterior, and lateral aspects of the left ventricle, however, may displace the loop upward and to the right, since the resultant vector due to infarction is most affected in such an example by the component due to infarction of the lateral aspect.

In the present study, the simultaneous recording of vectorcardiograms in the horizontal, sagittal, and frontal planes was extremely valuable in determining the

spatial distribution of electromotive forces. The horizontal plane was especially valuable for the analysis of precordial leads;[18] the sagittal plane for the analysis of V_F and multiple esophageal leads; and the frontal plane for the analysis of the unipolar and standard extremity leads. In each plane is recorded the projection onto that plane of the QRS sÊ loop. Any force acting essentially perpendicularly to a plane exerts little if any effect on the QRS sÊ loop in that plane (Fig. 20). Hence, an infarction of the diaphragmatic or inferior aspect of the heart does not appreciably affect the horizontal plane QRS sÊ loop; nor does an anteroseptal infarction affect the frontal plane QRS sÊ loop; nor a strictly lateral infarct affect the sagittal plane QRS sÊ loop. Electrocardiographic evidence of infarction may thus be confined to only one plane and may be lacking in the usual electrocardiographic leads. Spatial vectorcardiography offers an excellent method for the full electrocardiographic analysis of infarction and for obtaining information as to presumptive posterior infarction.

SUMMARY

1. Simultaneously recorded frontal, sagittal, and horizontal plane vectorcardiograms are described in sixty-seven persons with myocardial infarction.

2. The orientation of the QRS sÊ loops after infarction depended upon the localization of the infarcted area.

3. The vector loops in infarction are correlated with standard, unipolar extremity, multiple unipolar thoracic, and esophageal leads.

4. Spatial vectorcardiography as recorded by the technique employed in the present study is a superior method for the analysis of the spatial distribution of electromotive forces in infarction.

We wish to express our appreciation to Miss Thelma M. Shafran and Miss Edith Stern for technical assistance and to Mrs. Muriel Parsons for secretarial assistance.

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ANEURYSMS OF THE SINUSES OF VALSALVA

G. R. VENNING, B.M., M.R.C.P.

CARDIFF, WALES

ANEURYSMS of the sinuses of Valsalva (aortic sinuses) may be congenital or acquired. Congenital aneurysms are usually small, fingerlike projections or diverticula arising from the lowest part of the sinus, whereas acquired aneurysms may be much larger and may be diffuse dilatations of the sinuses, as in syphilitic aneurysms, or irregular cavities communicating with the sinuses, as in aneurysms complicating aortic valvular endocarditis or those apparently produced by dissection. The subject was reviewed by Morgan Jones and Langley,[12] who discussed in detail the difference between congenital and acquired aneurysms, and has also been reviewed independently by Raman and Menon.[15] It is the purpose of this paper to describe seven cases, of which three have been seen during life by the author; in one of these a correct ante-mortem diagnosis was made in a patient in whom a congenital aneurysm of the right coronary sinus of Valsalva ruptured into the right atrium. Clinical and autopsy reports, including histological study, and photographs and drawings in four cases in which the heart has been preserved as a museum specimen are presented. One feature of the syndrome of ruptured aneurysm is discussed which does not appear to have been noted previously and which is of importance in diagnosis. In considering the currently accepted theory of the embryological development of congenital aneurysms, a striking anomaly is noted and its implication discussed. Finally, the difficulty (noted by previous authors) of interpreting the pathological findings in the presence of endocarditis is discussed in particular relation to the present series of patients, in six of whom there was endocarditis.

CASE REPORTS

CASE 1.—A 56-year-old man was admitted to West Middlesex Hospital on June 17, 1948, with a history of progressive edema of the legs and dyspnea on effort for one month. On subsequent questioning he stated that he had become aware of a noise in his chest during this time. While in the Shanghai police force, he was medically examined on several occasions, the most recent being on retirement in 1933, and on no occasion was any comment made about his heart. There was no history of rheumatic fever or syphilis. On examination he was in gross congestive cardiac failure with massive edema, ascites, and right-sided hydrothorax. There was extreme venous congestion in the neck. The pulse was collapsing and regular, the rate being 116; the blood pressure was 250 to 270 mm. Hg systolic and 105 to 110 mm. Hg diastolic; the apex beat was in the fifth left intercostal space in the anterior axillary line, the cardiac impulse being heaving and forceful. There was a continuous murmur of great intensity, rough quality, and wide distribution, loudest in the third and fourth intercostal spaces at the left sternal border, where it was accompanied by a systolic thrill. Wassermann and Kahn tests were negative. The electrocardiogram showed right bundle branch block with first-degree heart block (P-R interval 0.23

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second) and auricular stress (P waves widened and bifid). X-ray screening on July 28, 1948, showed that there was great cardiac enlargement involving all chambers. The pulmonary arteries were very prominent, and expansile pulsation could be seen in the small intrapulmonary branches. There was posterior displacement of the barium-filled esophagus in the right oblique view. There was no evidence of calcification in the aorta or in the valves of the heart.

On treatment with salt restriction, mersalyl, and digitalization he had a profuse and prolonged diuresis and the body weight fell by 35 kilograms, from 93.7 kilograms to 58.7 kilograms, over a period of six weeks. As the edema subsided from the abdominal wall, the liver edge became palpable a handbreadth below the right costal margin. When the upper level of venous congestion in the neck was seen, the pulsation was noted to be of ventricular type. The combination of a collapsing pulse with the evidence of pulmonary hypertension shown on x-ray screening suggested a fistula between the aorta and the lesser circulation. The history suggested that this had developed recently with the onset of congestive failure; the expansile pulsation of the pulmonary artery branches together with the extreme venous congestion in the neck (comparable with that found in tricuspid incompetence) suggested that the leak from the aorta was into the right atrium.

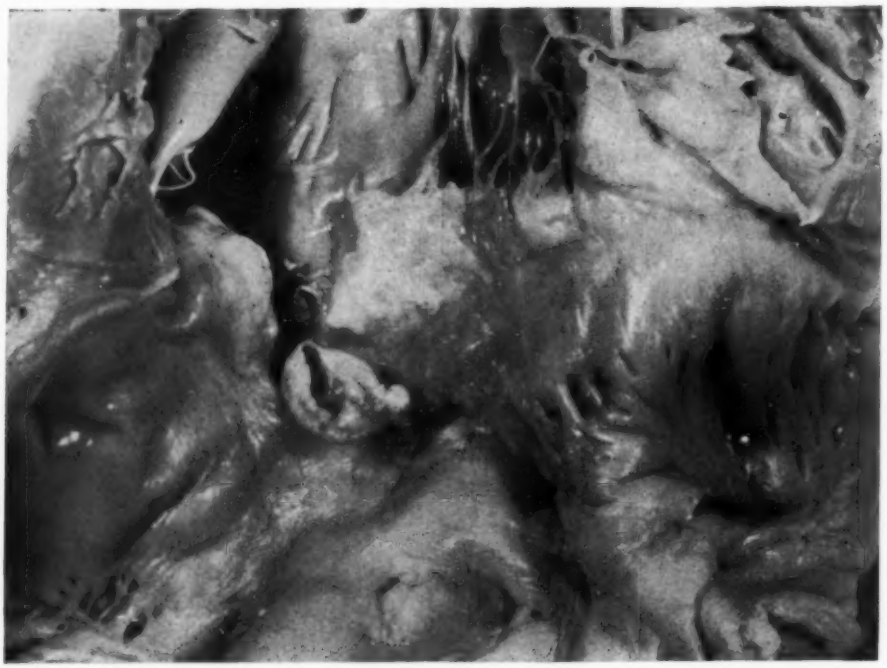


Fig. 1.—Close-up of the aneurysm projecting into the right ventricle. (Photograph by D. A. Vinten.)

Progress after the initial response to treatment was unsatisfactory. Signs of failure persisted, and following a respiratory infection in January, 1949, there was a relapse into gross congestive failure. In May he became progressively anemic, and the temperature was raised to 99° F. on several occasions and to 100° F. on one occasion. Bacterial endocarditis was suspected, but the occurrence of melena suggested an alternative cause for the anemia; although this was corrected by transfusion of packed red cells, the patient's condition slowly deteriorated and he died on July 19, 1949.

Post-mortem examination showed diffuse hemorrhage from the gastric mucosa and passive congestion of the viscera. The heart weighed 710 grams. There was hypertrophy of the left ventricle (25 mm.) and of the right ventricle (13 mm.), and the papillary muscles and columnae carneae were greatly hypertrophied. The pulmonary artery and pulmonary valves were normal.

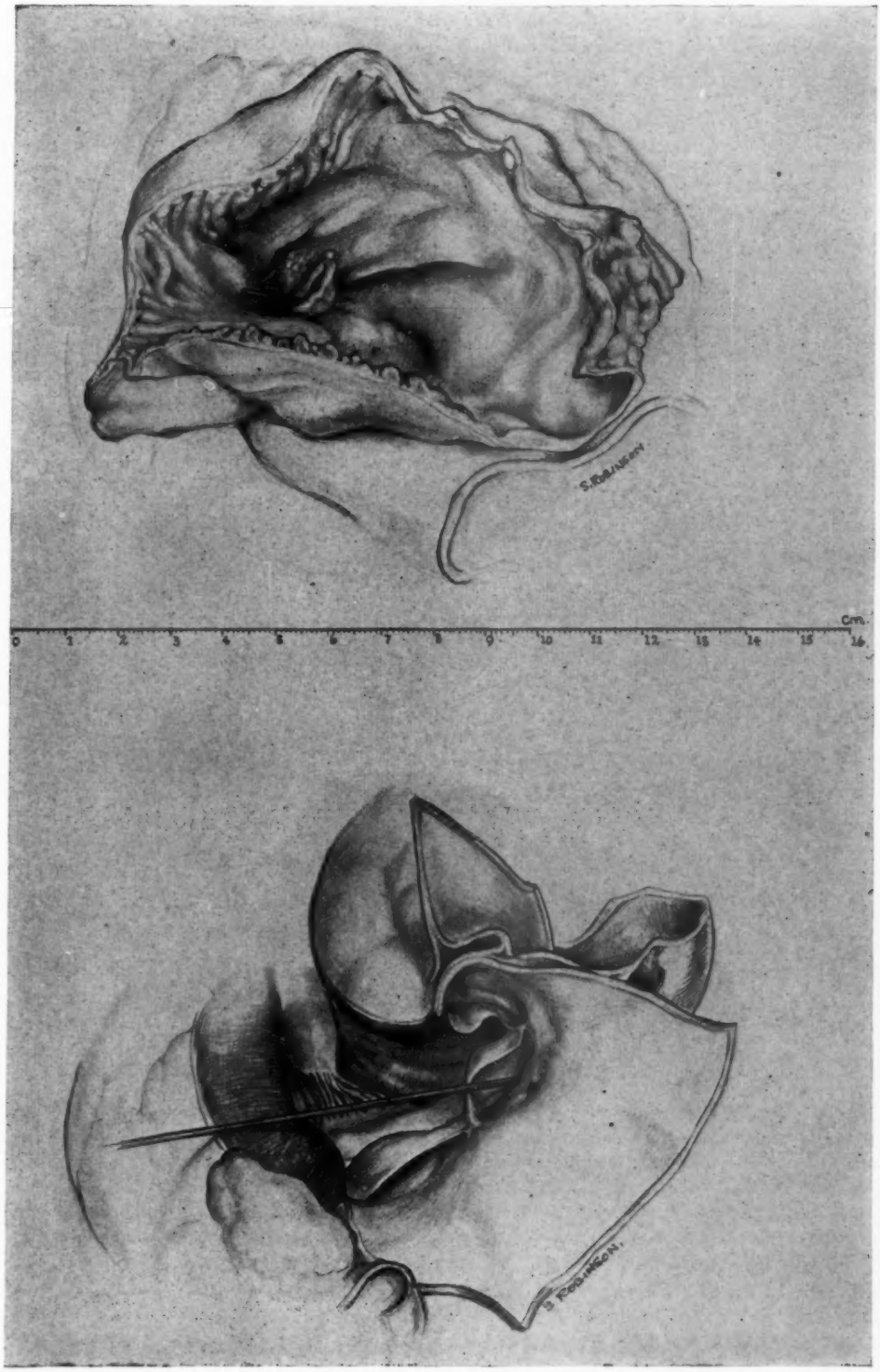


Fig. 2.—Right auricle (looking down on the tricuspid valve) to show the aneurysm. The aortic valve from above with the probe entering the aneurysm at the base of the right coronary cusp.

The aorta showed only slight atheroma in the first part and was normal in caliber and in thickness, and on histological examination there was no evidence of syphilis or of cystic medial necrosis. The aortic cusps were normal apart from slight fenestrations of the free margins of the left coronary and noncoronary cusps. The mitral valve was healthy and the left atrium slightly dilated. The right atrium was markedly dilated, and just above the junction of the septal and anterior cusps of the tricuspid valve at their attached border there was an aneurysm measuring 14 mm. by 10 mm. by 9 mm. with a linear rupture 9 mm. long and a small daughter aneurysm of 3 mm. in diameter.

Fig. 3.—Close-up of the mouth of the aneurysm at the base of the right coronary cusp of the aortic valve with the probe in situ. (Photograph by D. A. Vinten.)

The aneurysm had a smooth covering of atrial endocardium and a smooth lining. In the depth of the right coronary sinus of Valsalva there was a slitlike opening 6 mm. long opening into the aneurysm. The base of the right coronary cusp was thickened and included a small nodule of calcification approximately 3 mm. in diameter. Opposite the fish mouth rupture of the aneurysm there was a patch of thickening on the atrial surface of the septal cusp of the tricuspid valve. The aortic vestibule of the left ventricle and the pars membranacea septi were normal, as were the coronary vessels in their whole length.

CASE 2.—A 55-year-old woman was admitted to Hammersmith Hospital on Sept. 23, 1947, with a history of fever with shivering attacks four weeks previously, followed by symptoms of progressive cardiac failure. There was no relevant past or family history. On examination she was cyanotic and dyspneic with venous congestion in the neck with venous type of pulsation. The pulse was 126, regular, and collapsing in character. The apex beat was four inches from the

midline in the fifth left intercostal space. There were no thrills, but there was a loud, harsh systolic murmur at the apex and systolic and diastolic murmurs in the aortic area and down the left border of the sternum. There was poor air entry at both lung bases with impaired percussion note and crepitations. Both legs were edematous up to the knees, and there was a sacral pad of edema. The liver edge was not palpable. A chest roentgenogram showed the heart to be enlarged with bilateral basal congestion of the lungs. Treatment with salt-free diet, full digitalization, and mercurial diuretics was not followed by any improvement; ascites developed and by Oct. 10, 1947, the patient had gained 1 pound. The electrocardiogram at this time showed digitalis effects on the ST segment but no other abnormality. Southey's tubes were inserted

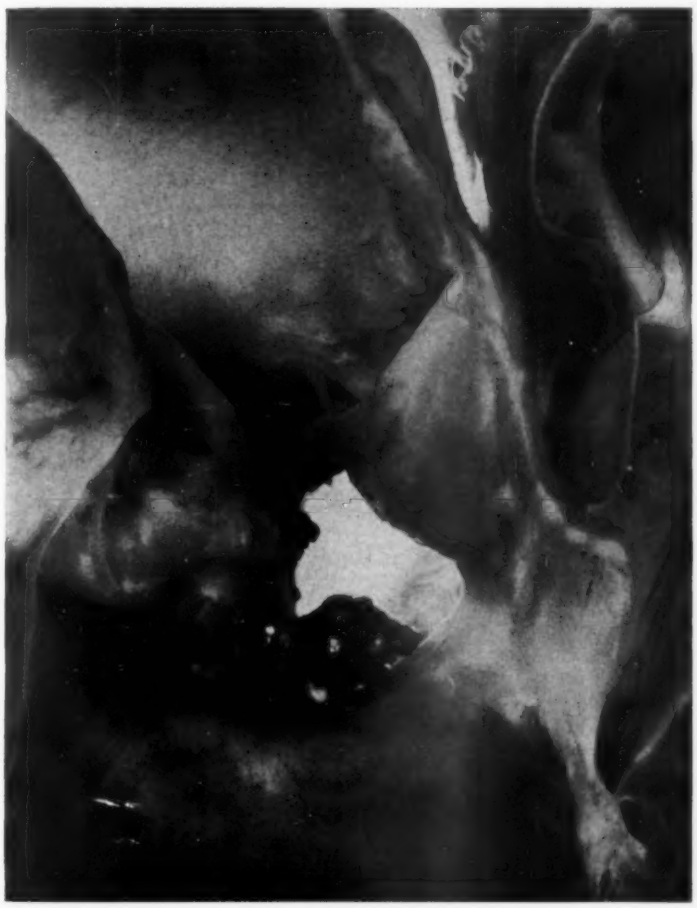


Fig. 4.—Bicuspid aortic valve with vegetations and the opening between the aneurysm and the left ventricle. (Photograph by E. V. Willmott.)

into the legs and drainage continued for seven days. At this time the blood urea was 144 mg. per 100 ml., and the temperature rose to 99° F. on one occasion. During the next month, the general condition deteriorated and the venous congestion increased. It was noticed that there was a ventricular type of venous pulse. The patient became drowsy and died in coma with a blood urea of 233 mg. per 100 ml.

Post-mortem examination showed passive congestion of the viscera. There were no emboli noted. The heart weighed 390 grams. The pulmonary and aortic valves were bicuspid, and there was infective endocarditis of the aortic valve. Below the origin of the right coronary artery a focus of infective endocarditis had destroyed the posteroinferior portion of the larger (posterior)

cusp, and the sinus of Valsalva related to this cusp was in communication with a cavity 3 cm. in diameter in the pars membranacea septi. The aneurysm bulged into the transverse sinus of the pericardium behind the first part of the aorta, into the outflow tract of the right pulmonary artery just below the bicuspid pulmonary valve, and to a lesser extent into the right atrium above the septal cusp of the tricuspid valve; at this point there was a small opening into the right atrium. There was another opening at the top of the cavity (at the base of the aortic cusp) leading into the cavity of the left ventricle. Both openings were lined with vegetations of endocarditis. *Streptococcus viridans* was subsequently grown from these vegetations. Histological examination showed no stigmata of rheumatism or syphilis. The sac was lined with thick fibrous tissue which contained calcium deposits, and similar deposits were present in the aortic cusps. No elastic tissue was noted in the walls of the sac.

These findings appeared to establish that the aneurysm in the pars membranacea septi preceded the endocarditis and not vice versa. The associated bicuspid pulmonary and aortic valves suggested a congenital origin with superimposed endocarditis, as in Abbott's case[1] and in uncomplicated cases of bicuspid aortic valves. If this aneurysm was congenital, it was considerably larger than previously reported congenital aneurysms, a finding which is not in keeping with the conclusions of Morgan Jones and Langley.[12] Even in retrospect it is difficult to see any indication of infective endocarditis apart from the symptoms at the onset. Apart from one reading of 99° F. there was no pyrexia during the patient's time in the hospital. There was a ventricular type of venous pulsation suggesting possible tricuspid incompetence (as in Case 1), and there was also a harsh precordial systolic murmur, which is a fairly constant finding in ruptured aneurysms. The patient was at no time fit for x-ray screening. The clinical diagnosis was aortic incompetence, presumably rheumatic, with congestive cardiac failure.

CASE 3.*—A 64-year-old man was admitted to Hammersmith Hospital on Aug. 11, 1943. Following an operation he had collapsed during convalescence and was treated with sulfapyridine (possibly for pneumonia). He was in the hospital four months with irregular fever, dyspnea, and nocturnal attacks of dyspnea. He lost 56 pounds during this period. There was a past history of rheumatic fever at the age of 8 years, but he was active and athletic as a young man. There was no relevant family history. Temperature was 98° F. Respirations were of the Cheyne-Stokes type, the rate varying from 24 to 38 per minute. He was orthopneic. The pulse rate was 100, blood pressure 120 mm. Hg systolic and 60 mm. Hg diastolic. There was finger clubbing and 2 to 3 cm. of venous congestion in the neck. The liver was enlarged three fingerbreadths below the right costal margin, and the spleen was just palpable below the left. The left plantar response was extensor. The main findings on investigation were: hemoglobin 94 per cent, white blood cells 8,000, polymorphonuclears 68 per cent, and blood sedimentation rate 73. A roentgenogram of the chest showed cardiac enlargement involving chiefly the left ventricle. The electrocardiogram showed left bundle branch block. There was temporary improvement with treatment until August 19 when the patient collapsed at 6:30 A.M. on waking and sitting up. He was cold, cyanotic, and pulseless, and the final clinical diagnosis was infective endocarditis of the aortic valve with congestive heart failure and terminal pulmonary embolism.

Post-mortem examination showed no evidence of pulmonary embolism. The heart weighed 540 grams, and there were 60 ml. of clear fluid in the pericardial sac. There were dilatation and hypertrophy of both ventricles and of the left auricle. The valves were normal except for the aortic valve which was rigid, thickened, and distorted by calcareous deposits. Near the right coronary cusp and extending into the left ventricular wall just anterior to the pars membranacea

*Abstracted from autopsy records.

septi was a small cavity filled with blood clot and having a ragged appearance. Histological examination showed that there was an acute inflammatory reaction around the sac, but that part of the lining of the sac was smooth and quite free from this reaction. The wall of the sac was thick and fibrous with calcification in the surrounding inflammatory tissue. A coronary artery branch appeared to open into the sac, and there was atheroma and calcification in relation to this branch. It appeared that infective endocarditis in relation to an aneurysmal sac in the interventricular septum below the right coronary sinus of Valsalva had caused a spread of acute inflammatory reaction into the tissue around the aortic ring. The case was discussed at a clinico-pathological conference at the Postgraduate Medical School, and no conclusion as to underlying etiology was reached. It was remarked that the absence of inflammatory tissue in part of the lining of the aneurysmal sac was against the infective endocarditis being entirely responsible and that there was probably some pre-existing aneurysm.

CASE 4.*—A 62-year-old man was admitted to a surgical ward in Hammersmith Hospital on Nov. 20, 1943, with acute retention of urine and died eleven days later with a clinical diagnosis of hypostatic pneumonia which had not responded to chemotherapy.

Post-mortem examination showed infective endocarditis of the aortic valve. The heart weighed 515 grams, the enlargement affecting chiefly the left ventricle. The valves were normal except for the aortic valve which was partly destroyed by ulcerative endocarditis. The right coronary sinus of Valsalva communicated with a cavity 12 mm. in diameter in the upper part of the interventricular septum, filled with thrombus. Histological examination showed that the cavity was a pus-filled diverticulum lined by fibrin. There was no fibrous tissue in the wall and no calcification, although there was a small area of calcification in the neighboring aortic cusp.

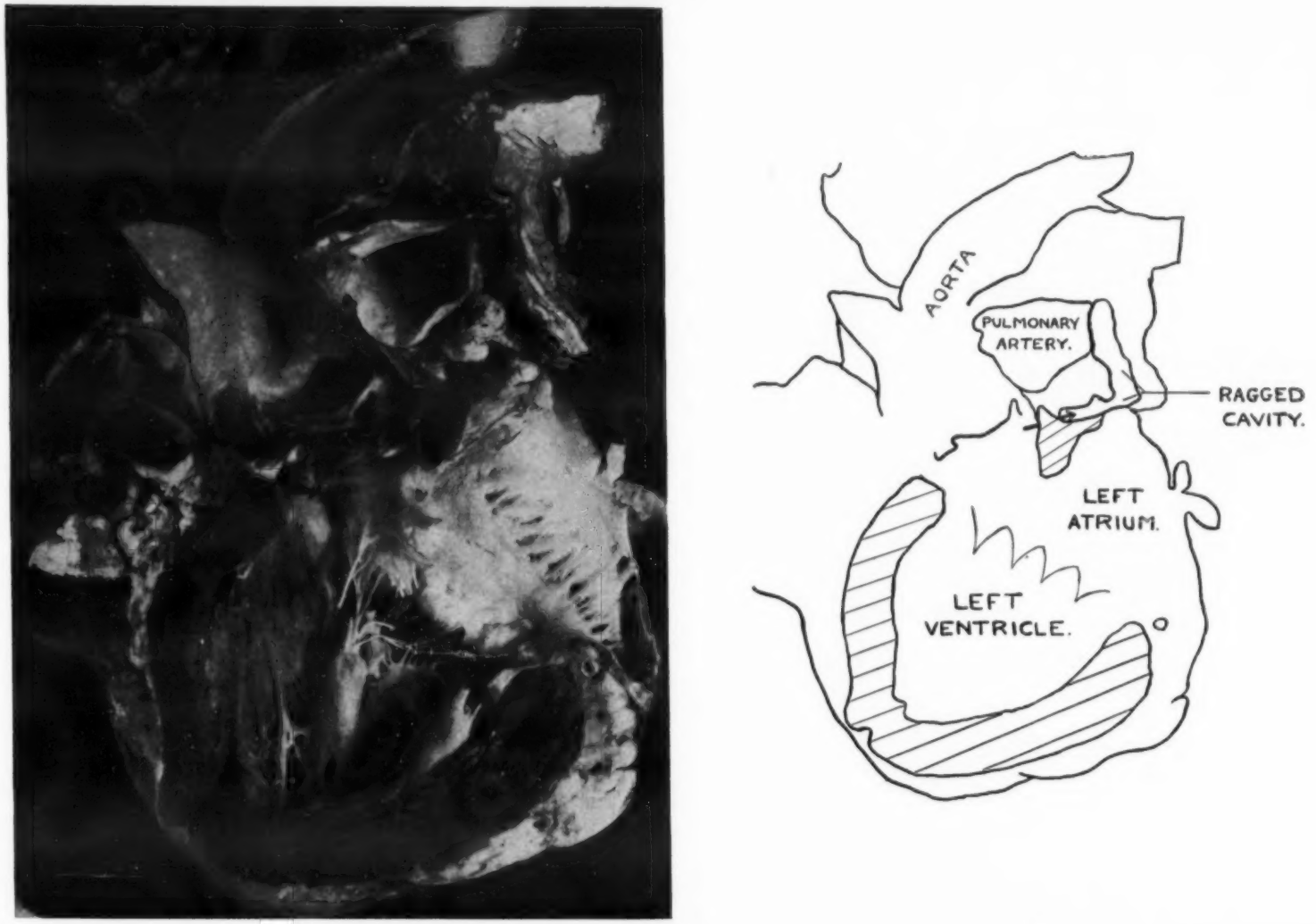
The pathologist (Dr. I. Doniach) was able to predict the presence of bundle branch block from the histological findings in the anatomical position of the atrioventricular bundle; this had, in fact, been recorded.

The findings in Cases 4 and 5 were regarded as representing ulceration with cavity formation in the neighborhood of the aortic ring as a result of acute endocarditis, leading to macroscopic appearances similar to congenital aneurysm of the sinuses of Valsalva with superimposed endocarditis, as in Case 2 and in several previously recorded cases. In Case 3 it was not possible to decide what sequence of events had taken place.

CASE 5.*—A 43-year-old man was admitted to Hammersmith Hospital on Dec. 25, 1945, with a history of extractions of some septic teeth six weeks previously. Two to three weeks after the dental treatment, he began to feel tired and after a further week had a rigor, began to run a fever, and complained of pains in the lumbar and scapular regions. For two days before admission he had precordial pain. There was a history of rheumatic fever at the age of 9 years with a recurrence at 10 years, following which he was told that he had developed "valvular disease of the heart." There was also a history of winter "bronchitis" for ten years. On examination the temperature was 100° F., and the pulse rate was 104 per minute; the pulse was collapsing in character and regular. The apex beat was four inches from the midline in the fifth left intercostal space. There was a systolic murmur accompanied by a thrill at the base with a diastolic murmur. There was finger clubbing. The total leucocyte count was 17,000 with 72 per cent polymorphonuclears. The electrocardiogram showed the Q_3 T_3 pattern of myocardial infarction. *Str. viridans* was grown from blood culture. On Jan. 3, 1946, the patient complained of diarrhea and collapsed and died suddenly.

Post-mortem examination showed subacute bacterial endocarditis. The heart weighed 660 grams, the enlargement affecting chiefly the left ventricle. The aortic orifice was stenosed, and there were recent fresh vegetations on the cusps. At the line of attachment of the right coronary cusp there was an opening from the aorta into a cavity filled with blood at the base of the interventricular septum which had extended to dissect the aorta away from the pulmonary artery

*Abstracted from autopsy records.



A. B.

Fig. 5.—Photograph of the heart (*A*) with tracing (*B*) to show the ragged cavity lying between the appendix of the left auricle and the left pulmonary artery and rupturing into the pericardium. (Photograph by G. R. Armstrong.)

for a distance of 1 cm. and had also extended along the interventricular sulcus surrounding the anterior descending branch of the left coronary artery which was occluded. Histological examination showed recent infarction of the left ventricular wall, and the blood-filled cavity was shown to be lined by the vegetations of subacute bacterial endocarditis. This case is similar to Case III in the series described by Morgan Jones and Langley.[12]

CASE 6.—A 44-year-old man was admitted to Cardiff Royal Infirmary on Dec. 23, 1946, with a fortnight's history of acute febrile illness with rigors. A week before admission his right arm "went dead," and on the day of admission he collapsed with severe pain in the chest. There was a history of two attacks of rheumatic fever before the age of 10 years and no other significant illness or family history. On examination he was almost moribund. He was sweating, pale, and had a grayish toxic appearance. He was stuporose, responding to pinprick, but not to commands. The temperature was 95° F. and the heart rate 140 and regular. The right radial pulse was impalpable, and the left was soft, not collapsing. The heart was enlarged to the left, the apex beat being in the anterior axillary line. There was a soft systolic murmur all over the precordium

Fig. 6.—Aorta showing the dilated sinus of Valsalva filled with vegetations. (Photograph by G. R. Armstrong.)

with a soft diastolic murmur down the left border of the sternum. The blood pressure was 125 mm. Hg systolic and 55 mm. Hg diastolic in the left arm and 115 mm. Hg systolic and 30 mm. Hg diastolic in the right arm. The right arm was colder than the left and was not moved by the patient. His condition deteriorated steadily, and he developed venous congestion in the neck; the blood pressure fell to 85 mm. Hg systolic. He died two days after admission. Blood cultures taken during life subsequently grew *Str. viridans*. The urine contained albumin, pus cells, and a moderate number of granular casts, and there was a polymorphonuclear leucocytosis of 36,400, rising terminally to 64,000.

Post-mortem examination showed the findings of bacterial endocarditis with septic embolism in the right brachial artery and in the intestines. The heart, including the arch of the aorta,

Fig. 5.—Photograph of the heart (*A*) with tracing (*B*) to show the ragged cavity lying between the appendix of the left auricle and the left pulmonary artery and rupturing into the pericardium. (Photograph by G. R. Armstrong.)

weighed 480 grams. There was a large hemopericardium, produced by the rupture of an aneurysm in relation to the anterior cusp of a bicuspid aortic valve which was affected by acute ulcerative endocarditis. The cavity of the aneurysm was filled with suppurating thrombus and was irregular in shape, apparently resulting from ulceration of the acute endocarditis into the tissues between the aorta, the pulmonary artery, and the left auricular appendix. There were no other findings of note in the heart.

CASE 7.*—A collier, 36 years old, was admitted to Cardiff Royal Infirmary on May 3, 1947, with one week's history of a febrile illness with pain in the front of the chest and dyspnea. On examination he was pale with sunken eyes, and the liver was noted to be enlarged and tender. The pulse was regular, rapid, and not collapsing; the blood pressure was 100 mm. Hg systolic and 80 mm. Hg diastolic. There was a soft systolic murmur heard all over the precordium. There was a leucocytosis of 31,000. In spite of intramuscular injections of 100,000 units of penicillin every three hours, his condition deteriorated steadily until death occurred eight days after admission.

Post-mortem examination showed hemorrhagic serofibrinous pericarditis with moderate-sized effusion. The heart weighed 620 grams. The aortic valve was stenosed, thickened, and calcified and apparently bicuspid. Large vegetations on the valve cusps extended down into dilated sinuses of Valsalva; that on the right was so dilated as to bulge into the outflow tract of the right ventricle. Microscopic examination showed that the whole thickness of the myocardium covering the dilated sinus of Valsalva was heavily infiltrated by acute inflammatory cells.

This case represents another variant of the type of aneurysm which may occur in bacterial endocarditis.

DISCUSSION

Diagnosis.—The correct diagnosis of congenital aneurysm of the sinus of Valsalva is unlikely to be made during life unless there is rupture into one of the chambers of the heart, and the diagnosis must then depend upon the alteration in hemodynamics. This holds true also for acquired aneurysms limited to the sinuses of Valsalva, but not, of course, for large syphilitic aneurysms which extend down incidentally into the sinuses, which should present no great difficulty. In his review of 4,000 cases of aneurysm, Boyd[3] pointed out that rupture most commonly takes place into the pericardium, less commonly into the superior vena cava or pulmonary artery, and rarely into the chambers of the heart. Morgagni[11] described many cases of rupture into the pericardium, but the first description of rupture into the pulmonary artery was by Wells.[21] The first correct diagnosis in life was by Wade,[19] and the syndrome has been reviewed recently by Nicholson.[13] The correct diagnosis of rupture into the right ventricle has been made seven times in cases of syphilitic aneurysm: Scott,[16] White,[22] Porter[14] twice, Herrmann and Schofield[6] twice, and Tompkins.[18] It has also been made on one occasion in a case of presumed congenital aneurysm with superimposed bacterial endocarditis by Abbott.[1] The correct diagnosis has not previously been reported in any case of congenital aneurysm uncomplicated by endocarditis, nor in any case in which rupture has taken place into the right atrium.

In none of the reported cases has the diagnostic importance of radioscopy been stressed, and Morgan Jones and Langley[12] in their recent review suggested that radiography will give little help in diagnosis. In Case 1 of this series in which a correct diagnosis was made in life, radioscopy was of great value in show-

*Abstracted from autopsy records. The heart was preserved as a museum specimen.

ing expansile pulsation of the small branches of the pulmonary arteries, similar to that seen in cases of atrial septal defect. This indicated hypertension in the lesser circulation, and as this was associated with all the signs of a free aortic regurgitation, there was good evidence of some unusual shunt, as was found to be the case. Rupture has occurred in a fair proportion of the reported cases and has not always been immediately fatal, so that radioscopy would seem to be of great importance in diagnosis, although at present this is of academic interest rather than of practical importance.

Embryology.—Abbott[1,2] drew attention to the events which occur in the embryo at the time of differentiation of the bulbus cordis into the outflow tracts of the right and left ventricles, the aorta, and the pulmonary artery and pointed out that failure of fusion of the proximal and distal bulbar swellings would lead to a congenital fistula between the aorta (right coronary sinus of Valsalva) and the outflow tract of the right ventricle just below the attachment of the pulmonary valve cusps (which develop higher up than the aortic valve cusps or further cephalad). Such a condition occurred in two cases described by Rickards and Charteris, quoted by Abbott.[1] A lesser degree of failure of the same fusion was put forward as a basis for the development of a congenital aneurysm of the right coronary sinus of Valsalva projecting into the right ventricle, and this hypothesis received support from the association of this lesion with the high ventricular septal defect which arises from the failure of fusion of the proximal bulbar swelling with the upper border of the ventricular septum. At that time all the known cases of congenital aneurysm had arisen from the right coronary aortic sinus and projected into the right ventricle. An analogy was drawn with the patent foramen Panizzae of the crocodile, which is a communication between the right ventricle and the left aorta just above the attachment of the valve cusps. Since that time, however, congenital aneurysms have been described similar in appearance but arising from the posterior (noncoronary) sinus of Valsalva and aneurysms projecting into the right atrium rather than the right ventricle (Goehring,[5] Duras,[4] Kawasaki and Benenson,[8] Herson and Symons,[7] Laederich and Poumeau-Delille,[9] and Case 1 of this series). Morgan Jones and Langley[12] in their recent article commented upon the occurrence of congenital aneurysms in the right coronary and noncoronary sinuses and pointed out that these are the two sinuses separated from the right ventricle and pulmonary artery by the fusion of the bulbar swellings. They did not, however, suggest how a failure of fusion of these swellings might lead to an aneurysm projecting into the left auricle. This difficulty is also avoided by Goehring,[5] who discussed the embryology at some length. At the stage of development at which the bulbar swellings fuse, the heart is still a hollow tube doubled up on itself to form an S bend, and the atria are separated from the bulbus cordis by a gap which represents part of the future pericardial cavity. As the heart acquires its adult shape later in development, the atria come to lie in direct anatomical relationship with those parts developed from the bulbus cordis, and in the adult heart the posterior part of the interventricular septum separates the cavity of the left ventricle from the right atrium and not from the right ventricle. This is shown clearly in the accurate drawing in Spalteholz' *Hand Atlas of Human Anatomy*[17] (Fig. 471 in the 1932 edition of

the translation). As the commissure between the right coronary and noncoronary sinuses lies above the posterior portion of the septum, it is clear that the posterior portions of the right coronary sinus and the noncoronary sinus lie in juxtaposition with the right atrium immediately above the attachment of the septal cusp of the tricuspid valve, and this is the site where congenital aneurysms may project into the right atrium. I am indebted to Dr. C. V. Harrison for the suggestion that the fundamental defect in cases of congenital aneurysm should be regarded as a defect in the development of the elastic tissue at the base of the aorta, and I think it is clear that the defect occurs later in development than the time of fusion of the bulbar swellings.

It still remains to consider those cases in which aneurysms occur in the left coronary sinus of Valsalva in the absence of any obvious pathological process. Micks[10] made out a case for regarding as congenital, aneurysms occurring in all three sinuses of Valsalva in the same patient and reviewed four other cases in which this occurred, but in which the pathological data were inadequate. Recently Raman and Menon[15] have reported a case, which they regard as congenital, in which aneurysms were found in the right coronary and left coronary sinuses. On the assumption that congenital aneurysms are due to defects in the fusion of the bulbar swellings, no cases in which an aneurysm is found in the left coronary sinus can be regarded as congenital, but if the defect is one which occurs later in development and involves the differentiation of the various tissues at the base of the aorta, there is no reason to rule out these cases for which it is difficult to account in any other way.

Pathology.—Morgan Jones and Langley have pointed out the difficulty there may be in deciding whether a given aneurysm shown at autopsy is congenital or acquired. This difficulty is particularly apparent when there is infective endocarditis as in Abbott's original case and in some cases in the present series. The presence of another congenital lesion is usually evidence that an aneurysm is congenital, but in Case 6 of this series the sequence of events appeared to be (congenital) bicuspid aortic valve—endocarditis—acquired aneurysm, which was really an abscess cavity produced by the endocarditis. In Case 2, on the other hand, an aneurysm associated with advanced ulcerative endocarditis was shown on histological examination to have a thick fibrous wall with calcareous deposits; it must have preceded the terminal endocarditis by a long time and was almost certainly congenital. Calcification has also been reported in association with presumed congenital aneurysms by Beck (quoted by Abbott[1]) and Duras[4] and is recognized as a frequent complication of bicuspid and quadricuspid aortic and pulmonary valves (Wauchope[20]).

SUMMARY

1. Seven cases of aneurysm of the sinus of Valsalva are reported, one congenital, two probably congenital with superimposed endocarditis, and four the result of endocarditis.

2. The importance of radioscopy in the diagnosis of the syndrome of ruptured aneurysm of the sinus of Valsalva is stressed.

3. The embryology and anatomy of the heart are discussed in relation to congenital aneurysms of the sinus of Valsalva.

4. The difficulty of interpreting the pathological findings in the presence of endocarditis is discussed.

I wish to thank Professor J. McMichael, Dr. Russell Fraser, Dr. N. F. Coghill, and Dr. William Phillips for permission to publish cases under their care and for their advice; Professor J. H. Dible and Professor J. Gough for permission to publish port-mortem data and for their advice; Dr. C. Harrison, Dr. I. Doniach, and Dr. A. C. Counsell for histological reports and advice; Dr. H. J. Anderson for his advice and stimulating teaching; and E. V. Willmott, D. A. Vinten, and G. R. Armstrong for photography and Miss S. Robinson for the drawings.

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CONGENITAL PULMONARY STENOSIS WITHOUT OVERRIDING AORTA

A Clinical Study

Y. Larsson, M.L., E. Mannheimer, M.D., T. Möller, M.L., H. Lagerlöf, M.D., and L. A. Werkö, M.D.

Stockholm, Sweden

THE designation "isolated pulmonary stenosis" should be used for those types of congenital malformations of the heart where there are signs of a pulmonary stenosis without an overriding aorta. In this respect isolated pulmonary stenosis differs essentially from pulmonary stenosis in the tetralogy of Fallot. The absence of right-to-left shunt as a rule protects the patient from cyanosis and makes a normal development possible in most cases without limitation of physical capacity.

Laubry and Pezzi[6] called attention to this benign type of pulmonary stenosis as early as 1921. In 1925, Müller[10] described three typical cases, stressing the similarity of symptomatology in this cardiac defect, patent ductus arteriosus, and ventricular septal defect.

Beyond these observations there have been few reports of cases of benign isolated pulmonary stenosis until recently Pollack,[11] Greene,[5] Cournand,[3] Mannheimer,[8] and Dow[4] with co-workers were able with the help of cardiac catheterization to demonstrate that pulmonary stenosis is a much more common malformation than was formerly believed.

According to our experience, benign isolated pulmonary stenosis is of the infundibular type in most cases. This makes an anatomical diagnosis at autopsy difficult, especially in mild cases, which may explain its rarity in post-mortem examinations despite its apparent frequency upon cardiac catheterization. The valvular pulmonary stenosis described by Allanby and Campell[1] and Mannheimer[8] we consider to be another, more serious, condition. It may be due to fetal endocarditis in contrast to the infundibular type. The prognosis is bad in such cases, and surgical treatment (valvulotomy, successfully introduced by Brock[2]) is indicated.

A clear anatomical definition of pulmonary stenosis is at present not possible. We have therefore found it more practical to give a physiological definition, pulmonary stenosis being present whenever intracardiac pressure measurements indicate a higher systolic pressure in the right ventricle than in the main stem of the pulmonary artery.

In a systematic study of 218 cases of congenital cardiac malformations by means of cardiac catheterization we have been able to diagnose isolated pulmonary stenosis in thirty cases.

From the Paediatric Clinic of Kronprinsessan Lovisa's Children's Hospital and the Fourth Medical Service of St. Erik's Hospital, Stockholm.

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METHODS

For the recording of electrocardiograms, phonocardiograms, and intracardiac pressure curves an Elmquist system electrocardiograph* was used, making possible simultaneous records of six tracings. Calibrated phonocardiography* was per-

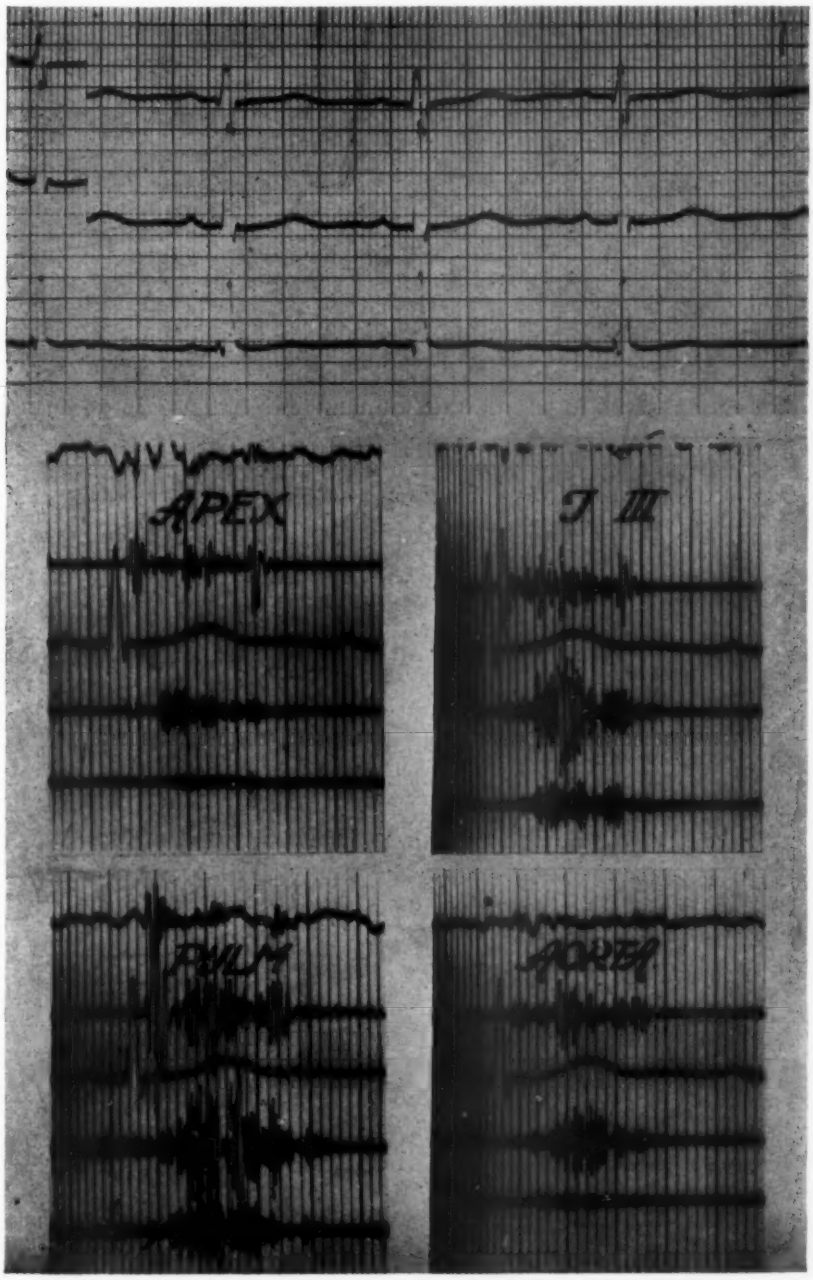

Fig. 1.

*Manufactured by the Elema Company, Stockholm-Hagalund, Sweden.

TABLE I. CLINICAL AND PHYSIOLOGICAL DATA FROM THIRTY CASES

NO.	SEX	AGE (YEARS)	SYMPTOMS	BLOOD PRESSURE IN ARM (MM. HG.)	HEMOGLOBIN (GM. %)	RED BLOOD CELLS (MILLIONS PER $MM.^3$)	BODY SURFACE ($M.^2$)	PA PRESSURE			RV PRESSURE		
								SYSTOLIC	DIASTOLIC	MEAN	SYSTOLIC	DIASTOLIC	MEAN
1	M	3 3/12		95/65	12.4	4.1					45	40	
2	M	4 3/12	Dyspnea on effort	95/55	13.1	4.3							
3	M	4 5/12		80/60	12.5	4.8		20	9		43	1	
4	M	4 11/12		115/75	11.2	3.7	0.8	19	10		33	2	
5	M	5 7/12		100/80	12.5	4.3		20	10	15	70	10	30
6	M	5 8/12		95/65	12.9	4.2	0.8	15	0		72	0	
7	M	5 9/12	Light dyspnea on effort	120/70	10.4	3.6		21	9		37	0	14
8	M	5 9/12		140/100	12.4	4.3	0.8	10	5		240	0	60
9	F	6 3/12	Dyspnea on effort	115/80	12.8	4.3		15			75		
10	F	6 8/12		125/75	12.2	4.2	0.7	30	14		94	6	60
11	F	7 8/12		110/75	13.0	4.3	0.9	13	5	10	50	0	15
12	F	8 4/12		110/70	12.5	4.0		16	8		71	0	
13	F	8 5/12		110/85	12.0	4.1		15	6	13	35	0	15
14	M	9 2/12		110/70	13.7	4.5	0.8	22	7		100	0	44
15	F	9 2/12		140/85	12.0	4.0		20	10	15	50	0	25
16	M	10 10/12	Dyspnea on effort	110/70	12.8	4.3		12	2	8	60	0	30
17	F	11 5/12	Dyspnea on effort; attacks of cyanosis	120/75	14.0	4.7	1.2	17	19		45	5	
18	F	11 8/12		120/75	13.0	4.1	1.1	5			75	0	25
19	F	12 5/12		135/80	14.6	4.8	1.2	17	4		170	0	49
20	F	12 5/12	Dyspnea and cyanosis on effort	125/65	14.1	4.6		30	6		100	2	
21	M	13 2/12	Dyspnea on effort	150/90	11.8	3.8		16	6		61	0	
22	M	13 7/12		115/70	13.1	4.3	0.2	20	9		31	5	
23	M	14 6/12		120/65	13.7	4.5		30	10	15	55	0	20
24	F	14 8/12		130/90	12.0	4.2	1.6	15	8	10	40	0	15
25	M	14 10/12	Dyspnea and cyanosis on effort	110/75	14.0	4.4		20	13	19	138	7	50
26	F	16 7/12	Palpitations	125/90	13.8	4.6				13			46
27	M	17 1/12		145/95				10	6		40	3	20
28	F	17 1/12		120/80	13.1	4.6		10			32	8	22
29	F	23 4/12		125/85	14.4	4.8		21	7	12	116	15	28
30	F	25		125/85	12.2	3.9	1.8	18	9	12	58	9	18

PA = Pulmonary artery main stem
RV = Right ventricle
RA = Right auricle
SVC = Superior vena cava
PV = Pulmonary vein

formed according to Mannheimer.[7] Unipolar chest leads were recorded according to Wilson.[14] Heart catheterization was carried out according to Cournand and the intravascular pressure measured with the apparatus designed by Tybjerg-Hansen and Warburg.[12] The arterial oxygen saturation during exercise was followed with the help of the oximeter of Millikan.[15] Venous angiocardiography was performed according to Sussman[13] under narcotal anesthesia with 70 per cent Diodrast. Regarding the details in technique of cardiac catheterization, the reader is referred to Mannheimer.[8] Only Cournand catheters No. 6 to 8 were used in the present series. Blood samples were taken from the different cham-

OF CONGENITAL PULMONARY STENOSIS WITHOUT OVERRIDING AORTA

CATHETERIZATIONS									
BLOOD GAS ANALYSES (VOLUME $\%O_2$)							OXYGEN INTAKE (C.C. PER MINUTE) 0-760 MM.	CARDIAC OUTPUT ACCORDING TO FICK (C.C. PER MINUTE PER M^2BS) (CALCULATED AS PULMONARY FLOW)	OXIMETER TEST FROM—TO (EXERCISE 1 MINUTE)
PA	RV	RA	SVC	PV (ASSUMED 95% O_2 CAP.)	CAPILLARY	SATURATION			
		11.4	11.8			92			92 → 92
		12.5	11.1						
11.8	11.6	11.0	13.3						95 → 94
11.3	10.7	9.6	10.0	14.2	15.0		146	5850	95 → 94
12.3	13.9	12.4	12.1						98 → 94
14.7	13.2	14.0	12.6	15.9	16.8	94	152	6900	
13.9	13.2	12.8	12.9						
12.1	11.8	12.0	12.2	17.1	18.5	95	157	3950	95 → 95
13.5	12.7	10.3	12.7						
14.8	13.7	12.9	13.6	19.1	20.1	96	142	7480	
12.7	12.6	13.4	12.0	15.4	16.3	92	159	5850	92 → 92
11.2	11.1	12.0	10.7			93			93 → 92
13.5	14.0	14.0	14.0						100 → 94
14.2	13.9	13.1	13.2	17.5		94	177	7690	94 → 93
12.9	12.5	12.5	12.1						95 → 95
14.7	14.7	14.2	13.6			87 ?			87 → 87
12.9	12.7	12.3	13.2	18.4	19.4	88	222	3360	88 → 84
15.3	15.9	15.0	14.8	17.8	18.8	98	140	4800	98 → 97
15.2	14.3	14.1		18.9	19.9	94	176	2920	
11.1	12.5	11.5	9.0			95			95 → 94
13.4	13.0	12.6	12.9			94			94 → 91
13.0	13.0			14.9	15.7	97	268	11500	
14.8	14.2	13.9	13.5						95 → 91
13.5	13.2	14.3	13.6	18.4	19.4	93	280	3500	93 → 90
13.7	(17.3)	13.9	13.1						95 → 93
12.5	12.2	12.9	11.9			86 ?			
13.5		13.2	13.6						
12.8	12.7	12.7	12.5						95 → 91
15.3	13.8	15.1	14.4			93			
12.4	12.3	13.1	12.0	17.3	18.2	93	209	2500	

bers and vessels, but the capacity of our laboratory did not permit more than one sample from each place.

RESULTS

Fifteen patients were female and fifteen were male. In Table I the data from each patient will be found. They were all acyanotic children or young adults without symptoms of cardiac disease. A few of them noted a slight dyspnea on exertion. A loud systolic murmur over the pulmonary orifice was the main reason for examination. On cardiac catheterization a right ventricular

hypertension could as a rule be established, the pressure here being on the average 73/3 mm. Hg and in the pulmonary artery 18/8 mm. Hg.

TABLE II. FREQUENCY OF SYMPTOMS AND AGE DISTRIBUTION

RIGHT VENTRICULAR SYSTOLIC PRESSURE (MM. Hg)	NUMBER	SYMPTOMS		AGE (YEARS)				
		PRESENT	NONE	0 TO 5	5 TO 10	10 TO 15	15 TO 20	20 TO 25
30–50	12	2	10	3	4	3	2	
51–100	12	4	8		6	5		1
> 100	4	1	3		1	2		1
Unknown	2	2		1			1	
Total	30	9	21	4	11	10	3	2

Table II gives the frequency of symptoms and the age distribution. The patients are grouped according to the degree of hypertension in the right ventricle. There is no correlation between the pressure in the right ventricle, the frequency of symptoms, or the age distribution.

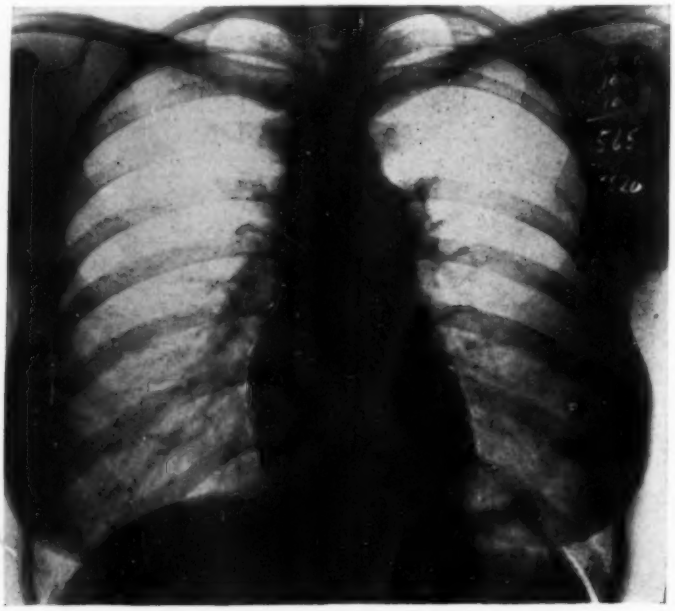

Fig. 2.

Fig. 1 shows the electrocardiogram and the calibrated phonocardiogram of a girl 6 years old with a slight right axis deviation and a very pronounced systolic murmur with the maximum intensity over the pulmonary orifice. The frequency range was 50 to 1,000 cycles per second.

Fig. 2 shows the x-ray picture of a woman 25 years old in whom the typical bulging of the pulmonary artery caused by poststenotic dilatation is apparent. The heart was of normal size in twenty-three cases but was slightly enlarged in seven cases.

TABLE III. CORRELATION BETWEEN PRESSURE IN THE RIGHT VENTRICLE AND CARDIAC ENLARGEMENT

RIGHT VENTRICULAR SYSTOLIC PRESSURE (MM. Hg)	HEART SIZE		ELECTRICAL AXIS			RIGHT VENTRICULAR HYPERTROPHY (WILSON)	
	NORMAL	ENLARGED	> +90°	< +90°	MEAN	PRESENT	ABSENT
30 – 50	10	2	4	7	72°	1	7
51 – 100	8	4	10	2	110°	6	3
> 100	3	1	3	1	79°	1	1
Unknown	2		2		113°	1	
Total	23	7	19	10	91°	9	11

In one case the electrical axis was unknown, and in ten cases a Wilson electrocardiogram had not been taken.

Table III shows that there is no correlation between the pressure in the right ventricle and the frequency of cardiac enlargement. If the ventricular hypertension is compared with the degree of right axis deviation in the electrocardiogram or with signs of right ventricular hypertrophy in unipolar chest leads according to Wilson, it is, however, evident that the higher the pressure in the right ventricle, the more pronounced the electrical right axis deviation.

Fig. 3 shows the mean angle of the electrical axis of all thirty patients (being +91 degrees) as compared with that in fifty patients with tetralogy of Fallot where the right axis deviation was more pronounced (+122 degrees) and with that in forty-two healthy children in whom the average angle of the electrical axis was +58 degrees.

Figs. 4 and 5 present typical pressure tracings. Fig. 4 is from a 6-year-old boy in whom the pressure in the right ventricle was 72/0 mm. Hg and in the pulmonary artery 15/0 mm. Hg, and Fig. 5 is from a woman 25 years old with a right ventricular pressure of 58/9 mm. Hg and a pulmonary artery pressure of 18/9 mm. Hg.

The results of the blood gas analyses are recorded graphically in Fig. 6. There was no regularly recurrent difference in the oxygen content of the blood in the superior vena cava, the right auricle, the right ventricle, or the pulmonary artery. The variations were within the limits of the normal variation of the method except in a few cases where a small intra-auricular or ventricular septal defect could not with certainty be excluded. Such small septal defects should not be of any functional importance, and the pulmonary stenosis dominated the picture. Neither the pressure findings nor the oxygen values had any similarity

to those found in cases of patent ductus arteriosus. Cardiac output was normal, and no significant difference was found between the systemic and pulmonary flows.

The arterial oxygen saturation was normal in all cases, the average value being 94 per cent. To prove the absence of a right-to-left shunt the arterial oxygen saturation was followed during exercise by means of a Millikan-Berg oximeter in nineteen cases. Fig. 7 presents the result of such a test as compared with the result from a case of tetralogy of Fallot. In pulmonary stenosis without overriding aorta and without any septal defects there is no fall in arterial oxygen saturation during exercise.

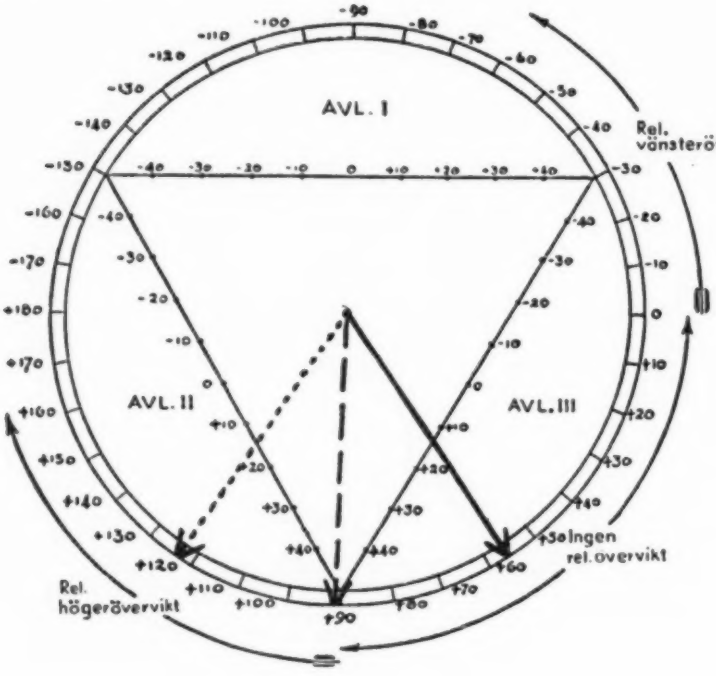

Fig. 3.

Venous angiocardiography was performed in eleven cases. In eight of these the diagnosis could be established by the demonstration of a distinct infundibular stenosis of the pulmonary artery and a poststenotic dilatation which in some cases was marked and had an aneurysmal character. There were no signs of intracardiac shunts and no secondary filling from the aorta of the pulmonary vascular bed as in patent ductus arteriosus. In one patient, a boy 5 years old, a poststenotic aneurysmal dilatation was present only in the right pulmonary artery (Fig. 8). The systolic murmur had in that case its maximal audibility

over the second right intercostal space, and an aortic stenosis had been suspected until heart catheterization and angiocardiography revealed the pulmonary stenosis and the poststenotic dilatation.

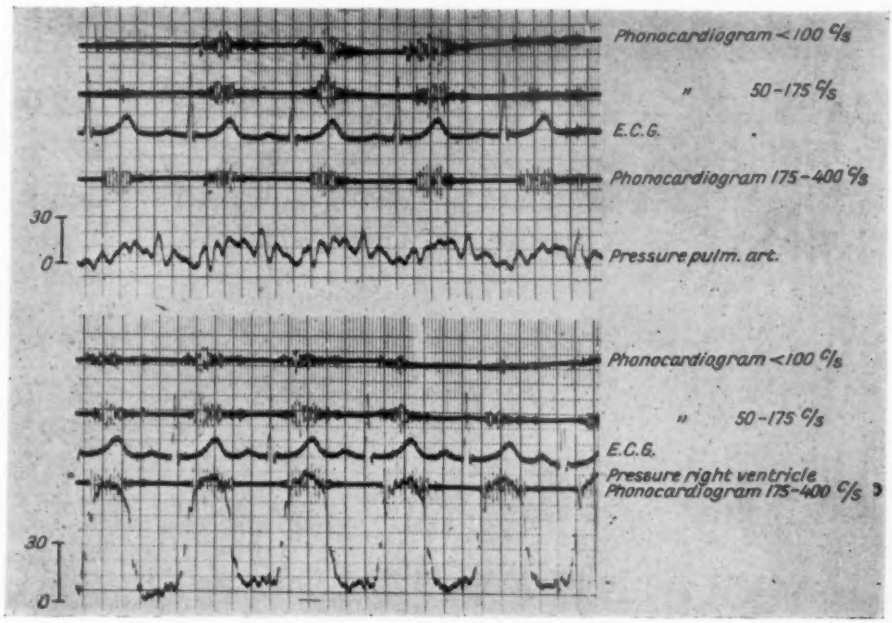

Fig. 4.

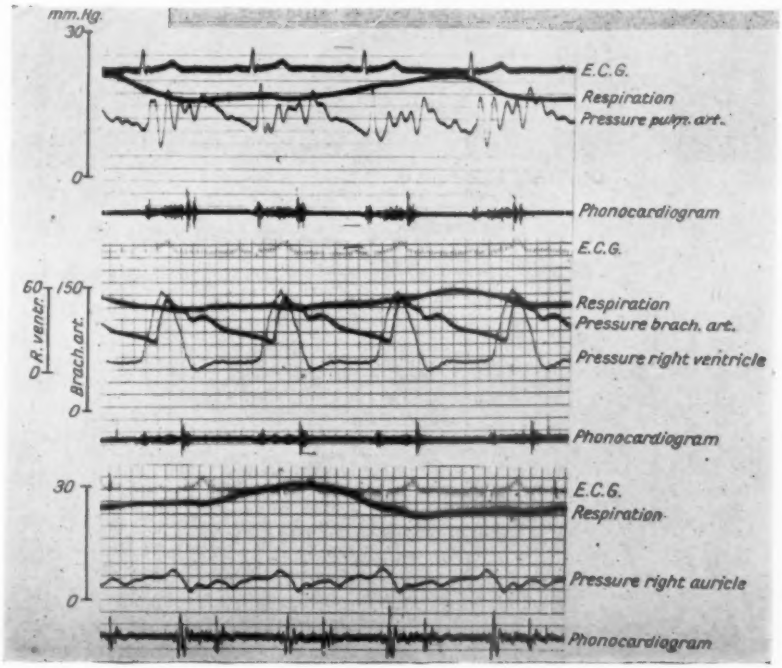

Fig. 5.

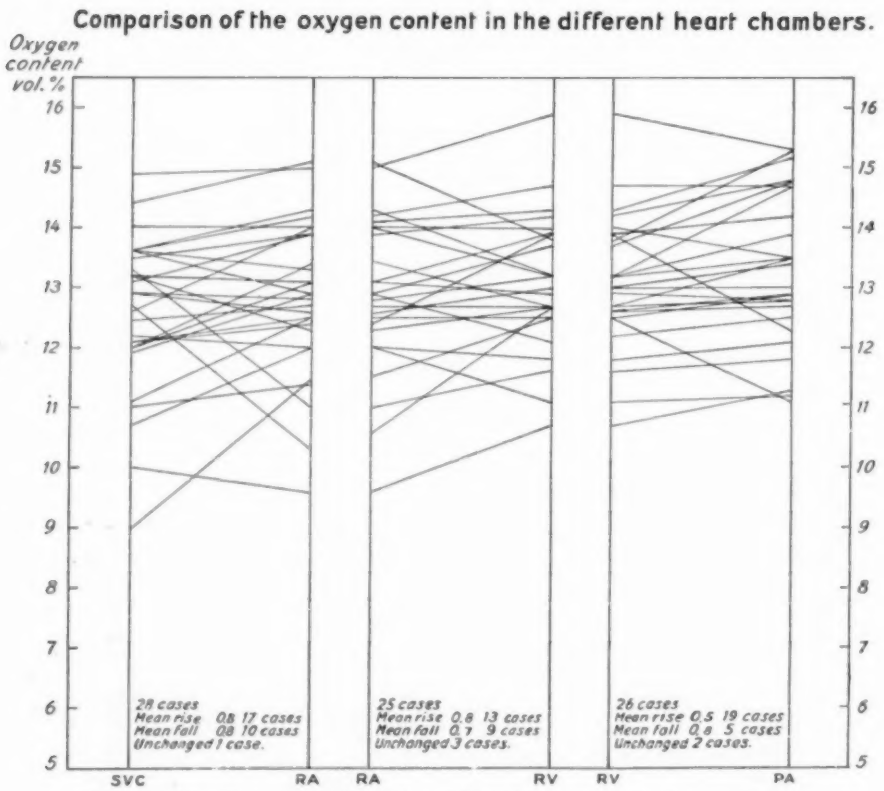
Comparison of the oxygen content in the different heart chambers.
Oxygen content vol. %
16
15
14
13
12
11
10
9
8
7
6
5
28 cases
Mean rise 0.8 17 cases
Mean fall 0.8 10 cases
Unchanged 1 case.
25 cases
Mean rise 0.8 13 cases
Mean fall 0.7 9 cases
Unchanged 3 cases.
26 cases
Mean rise 0.5 19 cases
Mean fall 0.8 5 cases
Unchanged 2 cases.
SVC
RA
RA
RV
RV
PA
SVC - Superior Vena Cava RA - Right Auricle RV - Right Ventricle PA - Pulmonary Artery

Fig. 6.

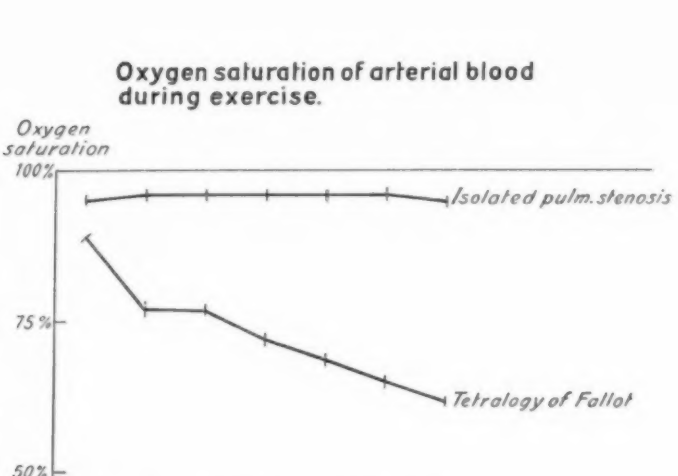
Oxygen saturation of arterial blood during exercise.
Oxygen saturation
100%
75%
50%
Isolated pulm. stenosis
Tetralogy of Fallot
0
10
20
30
40
50
60
Seconds

Fig. 7.

SUMMARY

There are reported thirty cases of isolated pulmonary stenosis. This condition seems to be more common than has been formerly believed. The cases displayed a uniform clinical picture and were similar to cases described by Greene and associates[5] and Dow and associates.[4] Clinical examination, electrocardiography, radiography, and cardiac catheterization showed typical signs of a pulmonary stenosis without overriding of the aorta. The patients were not cyanotic and had normal physical capacity. In most cases where the pressure in the right ventricle was only moderately increased, the prognosis seemed to be good without treatment. In patients with marked right ventricular hypertension surgical treatment (valvulotomy according to Brock[2]) should be seriously considered.

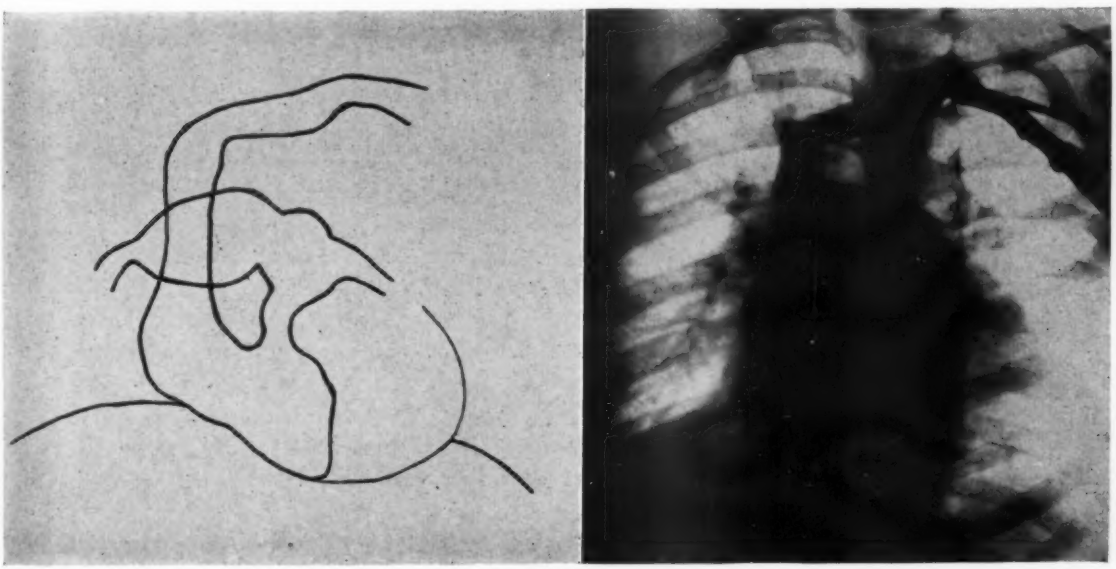

Fig. 8.

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THE VALUE OF THE ESOPHAGEAL ELECTROCARDIOGRAM IN THE ELUCIDATION OF POSTINFARCTION INTRAVENTRICULAR BLOCK

HOWARD B. BURCHELL, M.D., AND RAYMOND D. PRUITT, M.D.

ROCHESTER, MINN.

ELECTROCARDIOGRAPHIC investigators have maintained an indefatigable interest in the problems of intraventricular block, which term is generally used to include all forms of electrocardiograms with an abnormal duration of the initial ventricular complex. The historic and recent contributions to this field have been reviewed by Rosenman and co-workers.[1] There is a general acceptance of bundle branch block as such with recognized precordial patterns of right and of left bundle branch conduction defects.[2,3] The existence and mechanism of focal delays in ventricular excitation are of much more controversial nature. The term "arborization block" implying specialized conduction tissue localized to the endocardial area is probably misleading and if used by electrocardiographers requires specific definition in the manner in which it is used.

Focal intraventricular block may be classified into two types: the first, a delayed entrance and conduction into an area of acute injury; the second, a delay in the excitation of normal ventricular muscle distal to an area of recent or old injury. The first type may be occasionally observed as a transient phenomenon in either experimental or clinical acute myocardial infarction and is characterized by a wide, positive potential, tending toward a monophasic form which is recorded only from a restricted area either in a single direct or semidirect lead. The second type of focal intraventricular block is well recognized as a rather frequent finding following myocardial infarction and consists of increased duration of the QRS complex, not of a bundle branch block type, in electrocardiograms indicative of previous myocardial infarction.

Pruitt and co-workers[4] from experimental data have postulated that the apparently slow conduction of the excitatory process through the thickness of the ventricular muscle may be related to that process spreading transversely to the predominant direction of the muscle fibers. An implication that would be evident from this hypothesis is that infarction might destroy the continuity of the long parallel muscle fibers with the result that the excitatory process would be redirected into multiple muscle bridges and a much longer pathway would be followed to the remaining unscarred muscle syncytium. While the particular vulnerable areas of the myocardium which, when damaged, lead to increases of QRS duration are not defined, the thesis seems consistent with the observed facts. In the experience of one of us,[5] the esophageal electrocardiogram has been

From the Division of Medicine, Mayo Clinic, Rochester.
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of particular value in the diagnosis of a healed posterior myocardial infarction in the presence of right bundle branch block. In left bundle branch block characteristic tracings, supportive of the correct electrocardiographic interpretation, may be obtained; this has been well recognized since the initial work of Brown.[6] Within the past few years we have been recognizing with increasing frequency an electrocardiographic abnormality of the intraventricular block type which seems related to an abnormal delay in the excitation of the left ventricular base usually consequent to a posterior myocardial infarction. It has been the esophageal electrocardiogram that has allowed one to interpret the postinfarction intraventricular block pattern. Five cases have been chosen to illustrate this problem, and a sixth case is also described to illustrate that the incomplete pattern may be present in the absence of clinical evidence of heart disease.

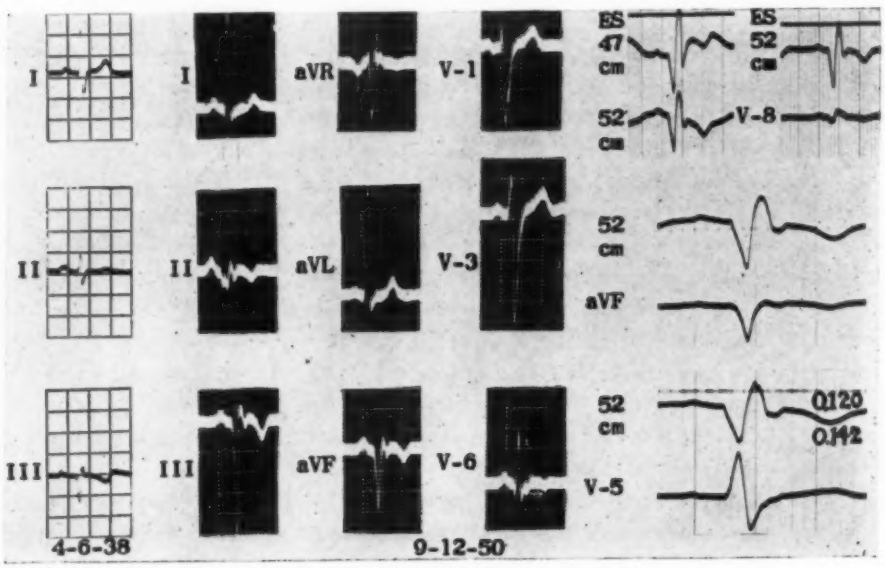

Fig. 1.—Electrocardiograms in Case 1.

CASE REPORTS

CASE 1.—A man, 54 years old, registered at the clinic in September, 1950, and gave the history that his blood pressure had been found to be elevated in 1948. In this year he had suffered an attack of severe precordial pain with circulatory collapse. The pain lasted three days. The patient's home physician had made a diagnosis of coronary occlusion, and the patient was kept in bed seventeen weeks. He had returned to light work but had had fatigability and precordial pain with effort. At the clinic his weight was 216 pounds and the blood pressure 170 systolic and 108 diastolic, expressed in millimeters of mercury. The general physical examination gave negative results otherwise. The roentgenogram of the chest showed moderate cardiac enlargement.

The electrocardiograms show the characteristic pattern of previous posterior myocardial infarction (Fig. 1). The late deflections in the QRS complex of aV_R and V_6 are to be particularly noted. In the column at the right, two leads were taken simultaneously. The marked delay in excitation of the left ventricular base is evident; at the 52 cm. level the "intrinsicoid" deflection occurred 0.12 second after the onset of the QRS, which measured 0.142 second in total duration.

It is apparent that the S wave in V_5 coincides in time with the R wave at the esophageal 52 cm. level. Neither Lead aV_F nor Lead V_8 reveals as clear a picture of the delayed excitation of the left ventricular base as does the esophageal tracing. The lower two records at the right were taken at triple the usual camera speed.

CASE 2.—A man, 47 years old, registered at the clinic in July, 1950, giving the history that in May, 1949, he had had a severe pain in the abdomen and was taken to the hospital where he remained for three weeks. The attending physician stated that the electrocardiogram showed a

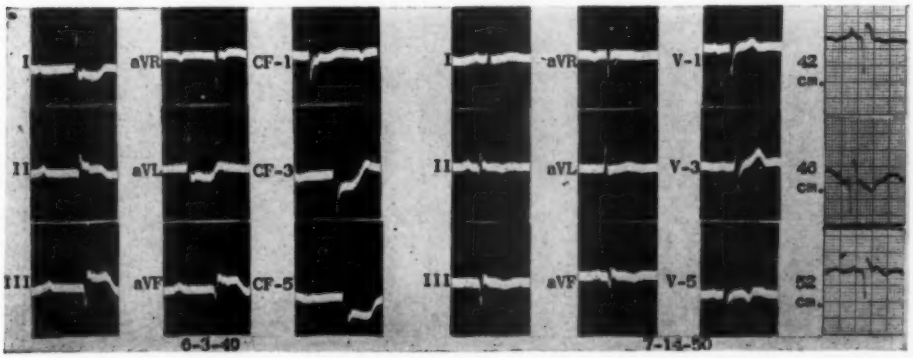

Fig. 2.—Electrocardiograms in Case 2.

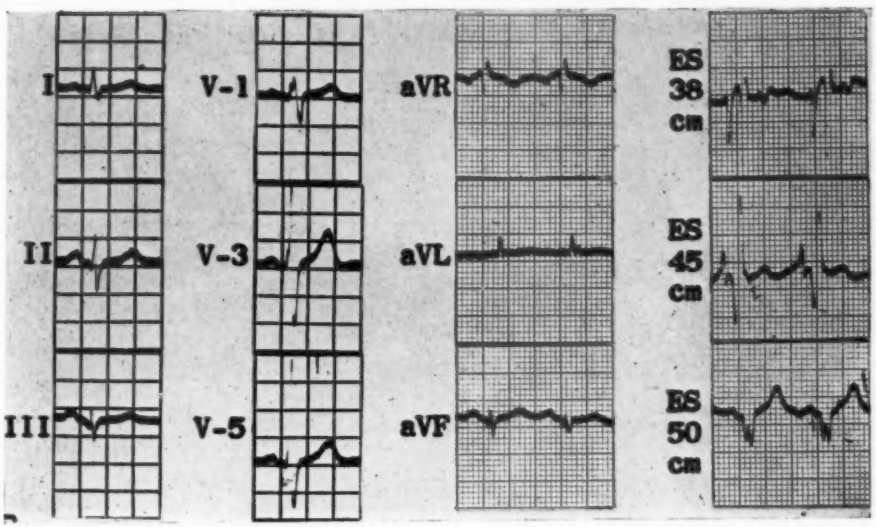

Fig. 3.—Electrocardiograms in Case 3.

"blood clot in the heart," and anticoagulant therapy was given. The pertinent findings in the examination were a homonymous hemianopsia, a blood pressure of 174 mm. Hg systolic and 104 mm. Hg diastolic, and evidence of arterial insufficiency in the legs. With the evidence of widespread arterial disease, the probability of Buerger's disease was considered likely. The roentgenogram of the chest was negative as were the general laboratory findings.

The electrocardiograms taken at the time of the acute myocardial infarction (June 3, 1949) and the following year (July 14, 1950) are shown in Fig. 2. The main features to be noted in the esophageal leads are the wide R waves of the QRS complex at both atrial and ventricular levels.

CASE 3.—A man, 56 years old, registered at the clinic in December, 1948, for an examination of the bladder; tumor of the bladder had been removed elsewhere. He had had an episode of pain in the anterior part of the chest lasting some hours in 1946. His blood pressure was normal, as were the results of general physical examination. The patient was seen again in July, 1949, because of a dermatitis; a diagnosis of pemphigus was made, and he was treated in the hospital for a month. The patient died from the severe dermatitis without any further chest pain in January, 1950. A post-mortem examination elsewhere was reported as showing a posterior myocardial scar measuring 1.5 by 1.5 cm. on the endocardial surface with the subendocardial fibrosis extending into the myocardium about 3 mm. The coronary arteries were atheromatous but patent.

The electrocardiograms (Fig. 3) reveal that the abnormal esophageal tracing at the 50 cm. level is the main indication of the old infarction later found post mortem. Although the QRS interval measured only 0.09 second, the configuration of several of the leads, the notched R of V_1, the deep S in V_5, and the prominent R of aV_R and at the ES 45 cm. level are particularly noteworthy.

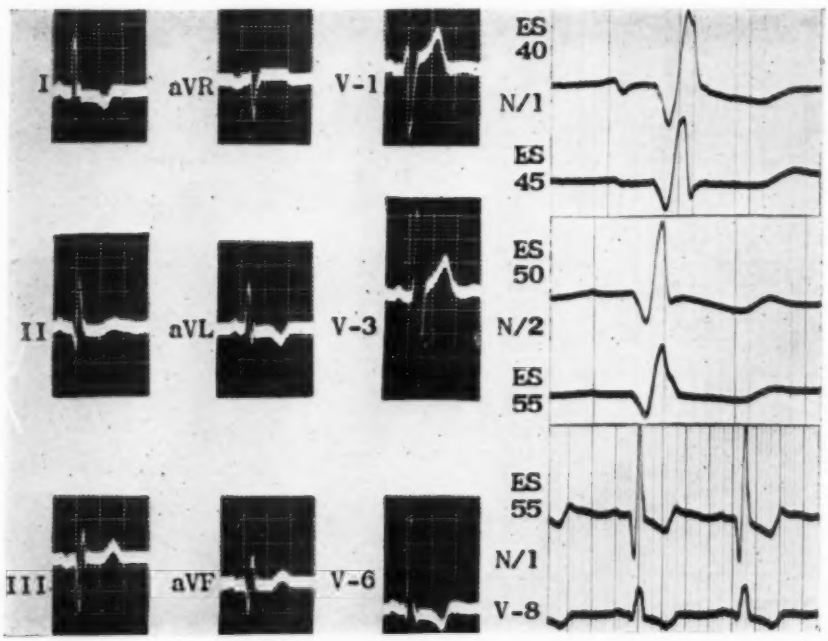

Fig. 4.—Electrocardiograms in Case 4.

CASE 4.—A man, 61 years old, registered at the clinic in August, 1950, with a history of typical anginal pain for four years. There had been no prolonged pain at any time to indicate clinically the occurrence of any myocardial infarction. The blood pressure averaged 150 mm. Hg systolic and 100 mm. Hg diastolic, and moderate obesity was present. The roentgenogram of the chest showed slight left ventricular enlargement. Routine laboratory findings were negative.

The electrocardiograms show abnormalities compatible with the diagnosis of previous posterior myocardial infarction (Fig. 4). The esophageal electrocardiograms are characterized by a high-voltage, wide R wave at both atrial and ventricular levels with the maximum QRS duration being 0.12 second. The abnormally late excitation of the left ventricular base rather than a usual QS deflection indicative of previous infarction characterizes the esophageal ventricular leads. The upper two records in the last column were taken at triple the usual camera speed.

CASE 5.—A man, 59 years old, registered at the clinic in November, 1950, and gave a history of known high blood pressure for six years, of a severe attack of abdominal pain lasting one and one-half hours in August, 1949, which was diagnosed and treated as a heart attack by the local

physician, and of chest pain on effort for the preceding three months. The blood pressure was 200 mm. Hg systolic and 105 mm. Hg diastolic. The roentgenogram of the chest showed moderate enlargement of the heart, particularly of the left ventricle.

The standard leads and extremity potentials were compatible with an old posterior myocardial infarction (Fig. 5). The QRS duration was 0.12 second. The esophageal electrocardiogram at the ventricular level was characterized by a wide R wave and a negative T wave, a configuration common to patients with left ventricular hypertrophy, but both the initial Q and the R wave were of greater duration than has been seen with hypertrophy alone. Of particular interest is the wide R deflection at the atrial level, where there is usually recorded a QR or QS deflection.

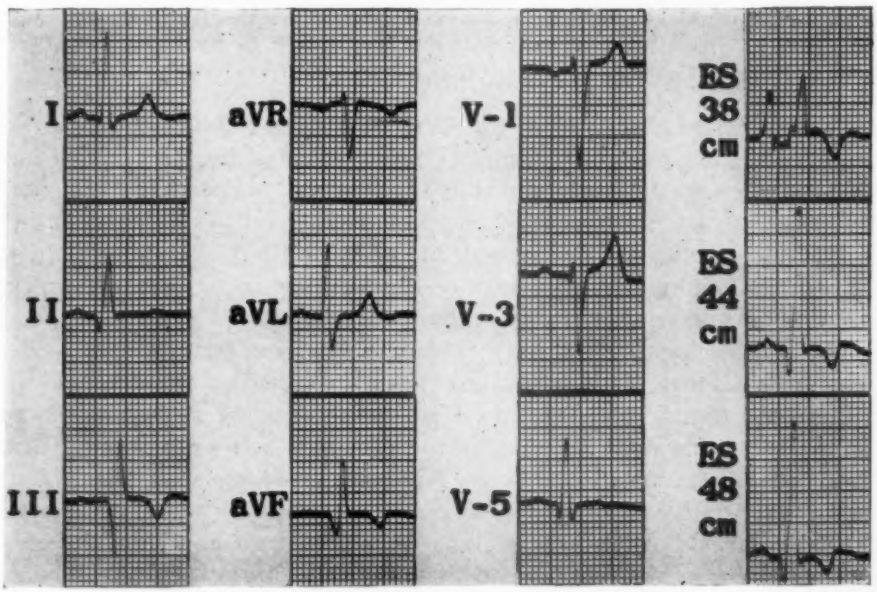

Fig. 5.—Electrocardiograms in Case 5.

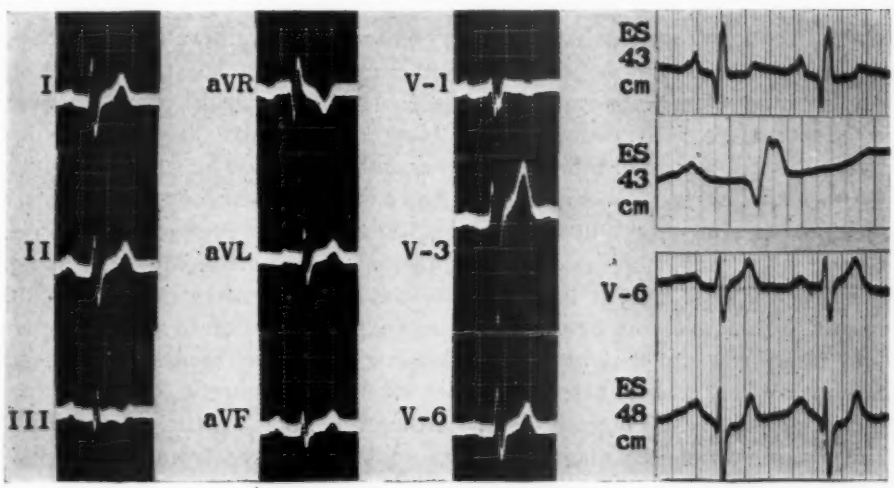

Fig. 6—Electrocardiograms in Case 6.

CASE 6.—A man, 27 years old, registered at the clinic in August, 1950, complaining of backache and fatigue. After an episode of transient faintness in 1943, he had visited a physician who suspected a cardiac abnormality because of the electrocardiogram. The standard lead electrocardiograms taken in 1945 kindly loaned by the home physician were essentially the same as those taken at the clinic in 1950. The results of routine laboratory tests and roentgenologic examination of the chest were normal.

In the electrocardiograms (Fig. 6) the QRS configurations of aV_R and V_6 were, in particular, suggestive of partial right bundle branch block, but that in V_1 was nonconfirmatory. S waves, recorded in V_6 and from deep in the esophagus (stomach), were isochronic. Electrocardiograms from the atrial level were characterized by a wide, notched R wave believed to be indicative of late activation of the base of the left ventricle in the neighborhood of the atrioventricular juncture.

COMMENT

It is to be noted that Wilson and co-workers[3] have published electrocardiograms under the nomenclature of infarction complicated by arborization block, in which the esophageal records (shown in their Fig. 40) are particularly similar to those in our Case 4. First and co-workers[7] have studied the incidence of intraventricular block following myocardial infarction and have introduced the new electrocardiographic term "peri-infarction block." Their conclusion that infarctions of the subendocardial region of the myocardium are responsible for the block would seem logical, but we feel that much more post-mortem evidence must be collected before the relationship is established as an invariable one. Excellent illustrations of esophageal electrocardiograms are included in some of their case reports, but none is similar to the picture which we have emphasized.

It is generally accepted that in the left ventricular free wall, the excitatory process has an over-all pattern of spread from endocardium to epicardium. The recent investigations of left ventricular cavity potentials have not altered this generalization concerning the spread of the excitatory process.[8,9] As in the normal heart the anterolateral and posterior walls of the heart are being depolarized simultaneously, it follows that the two parts of the ventricular wall will have a partial canceling or reducing effect on the potential recorded at a point either anterior or posterior subject to the effect of proximity. Any lesion that would delay the excitatory process reaching any part of the wall would alter the recorded electrocardiogram by disturbing the usual balancing of electromotive forces of the opposed walls, and larger potentials of opposite sign in sequence might be expected, with a resulting biphasic initial ventricular complex of increased duration. It might be stated that the excitation of the anterolateral and posterior walls was "out of phase." Since the basal part of the left ventricle is one of the last parts of the heart to be depolarized during the excitatory process, one could reason that abnormally late excitation of this part would be most easily recognized. Suppose that a lesion in the posterior apical myocardium caused such delay in the excitatory process reaching the basal portion of the left ventricle that the latter was not depolarizing during the spread of the excitatory process in the anterolateral wall but did depolarize after the excitatory process had been completed anteriorly. Then an electrocardiogram taken in the usual fifth precordial position would be of an RS form while one taken from the esophagus near the base of the left ventricle would be typically QR in configuration. Such

an explanation is offered for the observed precordial and esophageal electrocardiograms which have been labeled examples of intraventricular block following myocardial infarction. It is believed that this postinfarction pattern is a relatively common one and one that should be readily recognized and differentiated from the pattern of posterior myocardial infarction complicated by right bundle branch block.

SUMMARY AND CONCLUSIONS

Attention has been drawn to the value of esophageal leads in the elucidation of intraventricular block wherein there is delayed activation of the posterior basal portion of the left ventricle. The electrocardiograms of such patients may mimic incomplete right bundle branch block in the extremity and left precordial leads but not in the chest positions to the right of the sternum. The electrocardiographic picture of this type of intraventricular block is not infrequent and, while undoubtedly well recognized by some clinicians, it seems to deserve special emphasis for its universal recognition as postinfarction intraventricular block. While the pattern characteristically is the product of a previous occurrence of myocardial infarction, an example of slight intraventricular block of the same type is presented where the heart was clinically normal and the electrocardiographic aberration was considered to have no clinical significance.

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THE CONTRIBUTION OF THE AUGMENTED UNIPOLAR EXTREMITY LEADS TO THE PATTERN OF LEFT VENTRICULAR HYPERTROPHY IN THE HORIZONTAL OR SEMIHORIZONTAL ELECTROCARDIOGRAPHIC POSITION

NORMAN E. GOULDER, M.D., AND R. W. KISSANE, M.D.

COLUMBUS, OHIO

DELINEATION of the pattern of left ventricular hypertrophy in the standard leads of the electrocardiogram has depended largely on studies concerning axis deviation, amplitude of the QRS complex, and RS-T segment and T-wave abnormalities.[1-12] More recently, with the development of unipolar lead electrocardiography, Wilson and co-workers[11,14] and Goldberger[15,16] have described the qualitative features of the unipolar leads in well-developed patterns of left ventricular hypertrophy. Sodi-Pallares and associates[17] and Noth and Myers[18] have emphasized the significance of the delay of the intrinsicoid deflection in the unipolar precordial leads V_5 and V_6. In this problem Sokolow and co-wokers[19,20] and Schack, Rosenman, and Katz[21] have collected detailed quantitative data concerning the individual components of the ventricular complex in the unipolar leads. Although the past studies have helped clarify the pattern of left ventricular hypertrophy in the unipolar precordial leads (V leads), data concerning the augmented unipolar extremity leads (aV leads) have been less complete.

Measurements of the deflections in the aV leads are greatly dependent on the electrocardiographic position. There is great practical value in a quantitative study of the changes induced by left ventricular hypertrophy in the presence of the horizontal or semihorizontal electrocardiographic position (Wilson's criteria). The present study has been undertaken for the purpose of evaluating both the V and the aV leads in the electrocardiogram with this electrocardiographic position in two groups of patients, one with left ventricular hypertrophy and the other without this hypertrophy.

METHODS

The selection of tracings in this series has been based on the random appearance of electrocardiograms which were characterized by the horizontal or semihorizontal electrocardiographic position. These tracings included the 6 unipolar precordial leads and the 3 augmented unipolar extremity leads and fulfilled other criteria to be discussed. All tracings were omitted which showed evidence of myocardial infarction, questionable Q waves, low-voltage QRS complexes, or intraventricular block. No tracings were used from patients under digitalis or quinidine therapy, with an electrolyte disturbance, or with rhythms other than sinus. A case was considered normal if it met the following criteria: a standard

From the Division of Cardiology of the Department of Medicine, College of Medicine, Ohio State University, Columbus.

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lead electrocardiogram that was normal by all known requirements, a clinical examination that was negative for heart disease or hypertension, and a normal heart size by the teleroentgenogram or in some cases by the orthodiagram.

A case was considered compatible with left ventricular hypertrophy if it fulfilled the following criteria: a standard lead electrocardiogram meeting the requirements of left ventricular hypertrophy as formulated by Gubner and Ungerleider,[12] clinical evidence of a disease process known to effect left ventricular hypertrophy, and cardiac enlargement by the teleroentgenogram or in some cases by the orthodiagram. In applying the criteria of Gubner and Ungerleider, tracings were considered to represent left ventricular hypertrophy when the sum of R_1 and S_3 exceeded 22 mm., together with definite RS-T and T-wave abnormalities in Lead I.

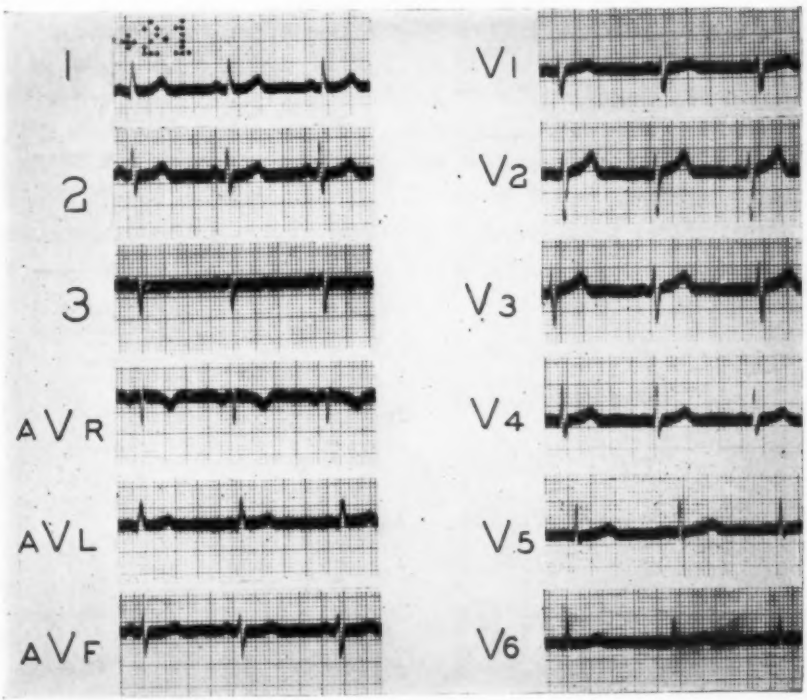

Fig. 1.—An example of the group of normal patients with the horizontal or semihorizontal electrocardiographic position. Left ventricular hypertrophy is not present. The precordial leads are inscribed with one-half normal standardization.

In all cases the 6 unipolar precordial leads were taken with the Wilson central terminal, and the 3 augmented unipolar extremity leads of Goldberger were taken with 5,000 ohms resistance in each extremity wire leading to the central terminal. In many instances the unipolar precordial leads were inscribed with one-half normal standardization (0.5 cm. equal to 1.0 mv.) in order to insure the recording of the total deflection.

Heart size measurements were based on the estimation of the frontal plane area from the long and broad diameters.[22,23] The heart was considered normal in

size if the frontal plane area was within 10 per cent of predicted normal value and was considered enlarged if the frontal plane area exceeded the predicted normal by 15 per cent or more.

The R, S, and T deflections of the ventricular complex were measured in each of the unipolar leads. Measurements were made with the aid of a magnifying glass and draftsman's calipers. The amplitudes were averaged when variation in amplitude was encountered due to respiratory influence. When the T wave was diphasic, it was measured as net amplitude of the position and negative deflections. Measurements made from unipolar leads inscribed with one-half normal standardization were doubled for tabulation. Appropriate corrections were made for minor technical errors in standardization.

RESULTS

The normal group consisted of 30 patients, of whom 16 were men and 14 were women. Ages ranged from 27 to 72 years, with a mean age of 46.9 years. The measurements obtained from the unipolar leads in this group are summarized in Table I, and a representative tracing is shown in Fig. 1. If these data are compared with those obtained by Sokolow and co-workers[19,20] in their group of normal subjects with left axis deviation, it is evident that they are similar.

TABLE I. AMPLITUDES OF WAVES IN NORMAL GROUP WITH THE HORIZONTAL OR SEMIHORIZONTAL ELECTROCARDIOGRAPHIC POSITION (30 CASES)

LEADS	R (MM.)			S (MM.)			T (MM.)		
	MINIMUM	MAXIMUM	MEAN	MINIMUM	MAXIMUM	MEAN	MINIMUM	MAXIMUM	MEAN
V_1	0	6.8	2.8	3.4	14.0	8.3	−2.0	3.6	0.5
V_2	1.4	10.8	4.8	4.0	16.8	11.2	−1.2	8.4	2.8
V_3	2.2	16.8	8.8	1.6	18.4	8.9	0.6	9.0	3.5
V_4	4.4	28.0	12.4	0	12.4	5.5	0.8	6.0	3.1
V_5	6.6	24.4	13.1	0	8.0	2.8	1.0	5.2	2.9
V_6	5.2	16.6	10.0	0	4.8	0.8	0.6	3.6	2.0
aV_R	0	3.4	0.7	0	12.0	6.2	−3.6	−1.0	−2.3
aV_L	5.4	10.6	7.3	0	1.8	0.2	0.6	3.6	1.4
aV_F	0.4	4.8	2.0	0.6	6.4	2.5	0	1.6	0.9

The left ventricular hypertrophy group consisted of 65 patients, all with the horizontal or semihorizontal electrocardiographic position. Of these patients, 27 were men and 38 were women. The ages ranged from 21 to 74 years, with a mean age of 55.8 years. The clinical diagnoses were hypertensive cardiovascular disease with a blood pressure consistently greater than 155 mm. Hg systolic and 95 mm. Hg diastolic in 59 cases, rheumatic heart disease with aortic stenosis in 1 case, rheumatic heart disease with aortic insufficiency in 1 case, rheumatic heart disease with predominant mitral insufficiency in 2 cases, and chronic glomerulonephritis with hypertension and chronic pyelonephritis with hypertension in 1 case each. Table II summarizes the measurements obtained from the unipolar leads of this group, and several representative tracings are demonstrated by Figs. 2, 3, and 4.

TABLE II. AMPLITUDES OF WAVES IN LEFT VENTRICULAR HYPERTROPHY GROUP WITH THE HORIZONTAL OR SEMIHORIZONTAL ELECTROCARDIOGRAPHIC POSITION (65 CASES)

LEADS	R (MM.)			S (MM.)			T (MM.)		
	MINIMUM	MAXIMUM	MEAN	MINIMUM	MAXIMUM	MEAN	MINIMUM	MAXIMUM	MEAN
V_1	0	7.2	2.2	6.0	36.0	18.3	−1.2	10.4	3.8
V_2	0	10.4	3.3	3.0	36.8	19.2	−0.6	18.8	4.5
V_3	0	24.8	6.8	1.6	38.8	15.0	−1.6	10.0	4.2
V_4	0.4	36.0	14.6	0	31.0	11.2	−4.4	8.0	2.8
V_5	6.0	36.4	20.8	0	24.4	5.5	−10.0	5.6	0.3
V_6	6.0	44.0	15.5	0	6.0	1.1	−13.6	3.6	−0.3
aV_R	0	4.0	0.9	0	19.4	7.7	−3.6	5.4	−0.7
aV_L	8.8	20.4	12.9	0	2.0	0.1	−6.8	2.4	−0.2
aV_F	0.2	8.2	2.4	0	14.2	6.0	−1.2	2.2	0.8

In comparing the normal group with the left ventricular hypertrophy group (L.V.H. group), it was felt that the amplitude of the R wave and the amplitude of the T wave in Leads V_5, V_6, and aV_L were particularly valuable. Of further interest in these leads was the ratio of the amplitude of the T wave to the amplitude of its associated R wave, expressed in percentage, and referred to as the T/R ratio.[24] The comparisons made between the two groups are summarized in Table III.

TABLE III. COMPARISON OF MEASUREMENTS IN NORMAL GROUP WITH THOSE IN THE LEFT VENTRICULAR HYPERTROPHY GROUP WITH THE HORIZONTAL OR SEMIHORIZONTAL ELECTROCARDIOGRAPHIC POSITION

LEADS	MEASUREMENTS	NORMAL GROUP			LEFT VENTRICULAR HYPERTROPHY GROUP		
		MINIMUM	MAXIMUM	MEAN	MINIMUM	MAXIMUM	MEAN
V_5	R (mm.)	6.6	24.4	13.1	6.0	36.4	20.8
	T (mm.)	1.0	5.2	2.9	−10.0	5.6	0.3
	T/R (%)*	10.8	40.9	22.1	−38.0	43.1	1.4
V_6	R (mm.)	5.2	16.6	10.0	6.0	44.0	15.5
	T (mm.)	0.6	3.6	2.0	−13.6	3.6	−0.3
	T/R (%)	10.4	36.2	20.0	−33.3	36.8	−1.9
aV_L	R (mm.)	5.4	10.6	7.3	8.8	20.4	12.9
	T (mm.)	0.6	3.6	1.4	−6.8	2.4	−0.2
	T/R (%)	10.3	50.0	19.2	−42.2	24.2	−1.6

*T/R (%) is the ratio of the amplitude of the T wave to the amplitude of the associated R wave expressed in percentage. When the T wave is negative, the T/R ratio is negative.

When the data in Lead V_5 were studied, the maximum amplitude of R_{V5} in the normal group was found to be 24.4 mm., and in the L.V.H. group R_{V5} exceeded 25 mm. in 17 patients, or 26 per cent of the total 65 patients. The lowest value for T_{V5} in the former group was 1.0 mm., and in the latter group T_{V5} was less than 1.0 mm. in 34 cases, or 52 per cent. The minimal value for the T/R

ratio in V_5 was 10.8 per cent in the normal group, and in the L.V.H. group the T/R ratio was less than 10 per cent in 43 cases, or 66 per cent of the group. In many cases the T/R ratio was even less than zero, due to the presence of a negative T wave.

Review of the data in Lead V_6 revealed that the maximum amplitude of R_{V6} in the normal group was 16.6 mm.; in the L.V.H. group R_{V6} exceeded 17.0 mm. in 20 cases, or 31 per cent. The lowest amplitude of T_{V6} was 0.6 mm. in the normal group, and T_{V6} in the L.V.H. group was less than 0.6 mm. in 38 cases, or 58 per cent. The minimal value for the T/R ratio in V_6 was 10.4 per cent in the normal group, and in the L.V.H. group the T/R ratio in V_6 was less than 10 per cent in 47 cases, or 72 per cent.

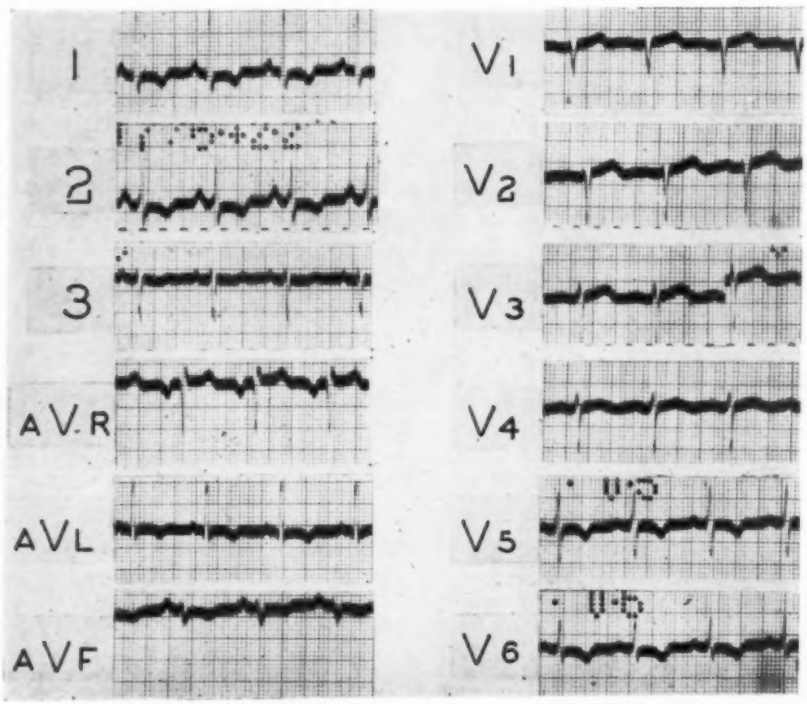

Fig. 2.—An example of the group of patients with left ventricular hypertrophy in the presence of the horizontal or semihorizontal electrocardiographic position. Note that Lead aV_L shows an R wave of 10.4 mm. and a T/R ratio of less than zero due to a negative T wave. The precordial leads are inscribed with one-half normal standardization.

In Lead aV_L the highest amplitude of R_{AVL} in the normal group was 10.6 mm., and R_{AVL} in the L.V.H. group exceeded 11 mm. in 41 cases, or 63 per cent. In the former group T_{AVL} had a minimum amplitude of 0.6 mm., and in the latter group it was less than 0.6 mm. in 48 cases, or 74 per cent. The T/R ratio in the normal group reached 10.3 per cent as the lowest value, and in the L.V.H. group it was less than 10 per cent in 55 cases, or 85 per cent.

Since the highest incidence of abnormalities was evident in Lead aV_L, further study was made of this lead. The findings are listed in Table IV. Of the 65 patients in the L.V.H. group, 41 had an R wave greater than 11 mm., and 24 had

an R wave which was in the range of the higher values for R_{AVL} in the normal group. Of the 41 patients with an R wave greater than 11 mm. in Lead aV_L, 35 also had a T/R ratio less than 10 per cent, and 6 had a T/R ratio greater than 10 per cent. Of the 24 patients with an R wave less than 11 mm., 4 manifested an R wave 8.8 to 9.0 mm., 7 had an R wave 9.0 to 10 mm., and 13 demonstrated an R wave 10 to 11 mm., but in all 24 the T/R ratio was less than 10 per cent. Thus, in all cases where R_{AVL} in the L.V.H. group overlapped the higher values for R_{AVL} in the normal group, the T/R ratio in aV_L was less than 10 per cent, a finding which never occurred in the normal group for the range of R waves encountered.

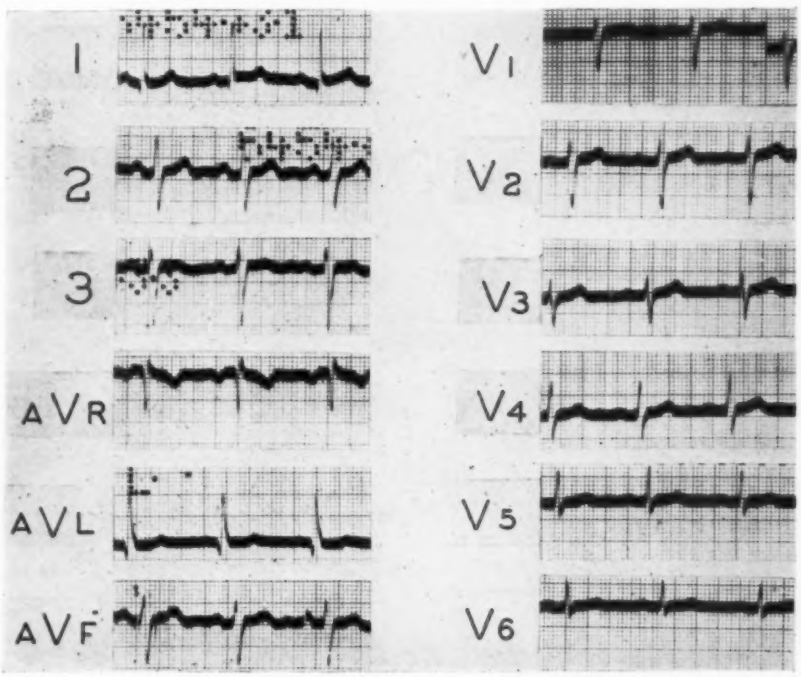

Fig. 3.—An example of the group of patients with left ventricular hypertrophy in the presence of the horizontal or semihorizontal electrocardiographic position. Note that Lead aV_L shows an R wave of 10.6 mm. and a T/R ratio of less than 10 per cent and is more diagnostic for left ventricular hypertrophy than Lead V_5 or Lead V_6. The precordial leads are inscribed with one-half normal standardization.

Consequently, in Lead aV_L an R wave greater than 11 mm. together with a T/R ratio less than 10 per cent was present in 35 of the total 65 patients, or 54 per cent; an R wave greater than 11 mm. without a low T/R ratio was present in 6 additional patients, or 9 per cent; an R wave of 10 to 11 mm. together with a T/R ratio less than 10 per cent was present in 13, or 20 per cent. In the remaining 11 patients, or 17 per cent of the total group, there was an R wave at the lower limit of 8.8 to 10.0 mm. with a T/R ratio less than 10 per cent. Thus, in 83 per cent of the patients with left ventricular hypertrophy with the horizontal or semihorizontal electrocardiographic position, Lead aV_L was characterized either by an R wave greater than 11 mm., with or without a T/R ratio less than 10 per cent, or by an R wave greater than 10.0 mm. always with a T/R ratio less than 10 per cent.

DISCUSSION

From this study it appears that Lead aV_L has particular significance in an evaluation of the presence or absence of left ventricular hypertrophy in the tracing of a patient with the horizontal or semihorizontal electrocardiographic position. In this situation the potential variations of the left ventricle are transmitted particularly well to the left arm, and in left ventricular hypertrophy uncomplicated by other significant disease processes Lead aV_L manifests an R wave of high amplitude with a T wave that is inverted or that is abnormally low relative to its associated R wave, a relationship that is crystallized by a low T/R ratio.

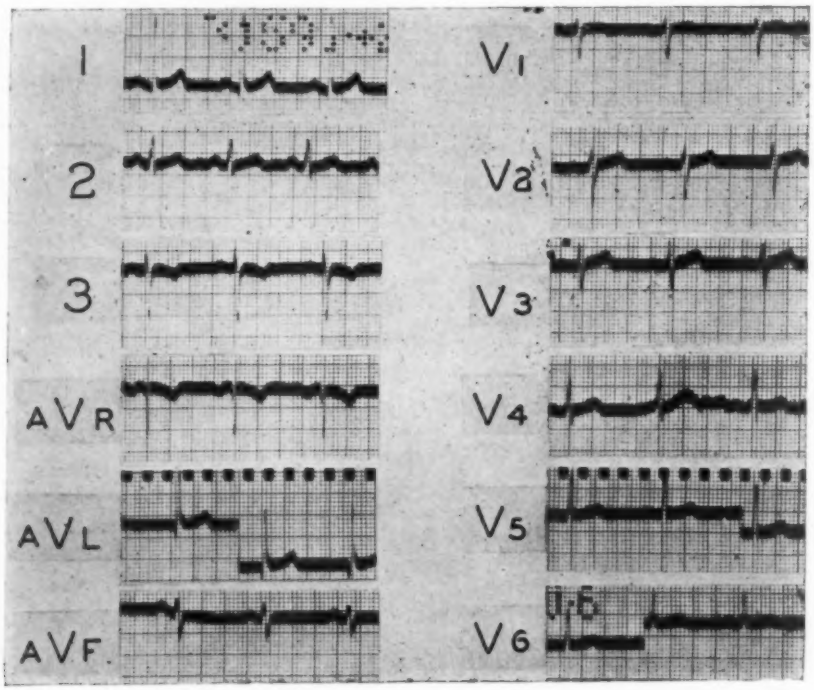

Fig. 4.—An example of the group of patients with left ventricular hypertrophy in the presence of the horizontal or semihorizontal electrocardiographic position. Note that Lead aV_L shows an R wave of 12 mm., although the T/R ratio exceeds 10 per cent. The precordial leads are inscribed with one-half normal standardization.

It is to be emphasized that this abnormal pattern may be evident in Lead aV_L even when the unipolar precordial lead pattern is within normal limits (see Figs. 3 and 4). Although Lead aV_L may not present a diagnostic pattern in all cases of left ventricular hypertrophy, it appears to record a greater incidence of abnormalities suggestive of left ventricular hypertrophy than Leads V_5 and V_6 when the electrocardiographic position is horizontal or semihorizontal.

Grant's[25] study of the spatial vector electrocardiogram presents a theoretical basis for this observation, for in the horizontal or semihorizontal electrocardiographic position the spatial vector of the ventricular potentials is often best projected on the left arm lead. The evaluation of left ventricular hypertrophy,

therefore, should routinely include the unipolar limb leads as well as the unipolar precordial leads; otherwise, the significant pattern for left ventricular hypertrophy may be missed, or else left doubtful. When the electrocardiographic position is horizontal or semihorizontal, the diagnostic pattern for left ventricular hypertrophy should appear in Leads V_5, V_6, or aV_L. One may place emphasis not only on the amplitude of the R wave but also on the relationship of the T wave to the amplitude of the R wave in a given lead. Thus, a T wave need not be considered low in terms of absolute values, but low in relation to its associated R wave. Wilson and co-workers[26] have pointed out that the area under the QRS complex bears a significant relationship to the area under the RS-T and T complex. Such a relationship may exist in a definite manner in left ventricular hypertrophy. It is felt that the T/R ratio, though expressed in terms of amplitude in the present study, may approximate the area relationship between the initial and terminal components of the ventricular complex in left ventricular hypertrophy.

TABLE IV. INCIDENCE OF SIGNIFICANT FINDINGS IN LEFT VENTRICULAR HYPERTROPHY WITH THE HORIZONTAL OR SEMIHORIZONTAL ELECTROCARDIOGRAPHIC POSITION

		NO. CASES	PERCENTAGE OF GROUP
Lead V_5	R greater than 25 mm.	17	26
	T less than 1.0 mm.	34	52
	T/R less than 10%	43	66
Lead V_6	R greater than 17 mm.	20	31
	T less than 0.6 mm.	38	58
	T/R less than 10%	47	72
Lead aV_L	R greater than 11 mm.	41	63
	T less than 0.6 mm.	48	74
	T/R less than 10%	55	85
Combined criteria in Lead aV_L	R greater than 11 mm. with T/R less than 10%	35	54
	R greater than 11 mm. with T/R greater than 10%	6	9
	R 10.0 to 11 mm. with T/R less than 10%	13	20
		54	83

SUMMARY

1. The unipolar precordial and augmented unipolar extremity leads were studied for the values of R, S, and T waves in 30 normal subjects presenting the horizontal and semihorizontal electrocardiographic positions and in 65 patients with left ventricular hypertrophy with a similar electrocardiographic position.

2. The instances where the measurements in the left ventricular hypertrophy group fell outside the range of measurements in the normal group were tabulated for the most useful leads, V_5, V_6, and aV_L. A particularly valuable measurement was the ratio of the amplitude of the T wave to the amplitude of its associated R wave in a given lead, expressed in percentage and called the T/R ratio.

3. Of the 65 patients with left ventricular hypertrophy 83 per cent were characterized in Lead aV_L either by an R wave greater than 11 mm. with or without a T/R ratio less than 10 per cent, or by an R wave greater than 10 mm. always with a T/R ratio less than 10 per cent.

4. These findings emphasize the value of Lead aV_L in establishing the pattern of left ventricular hypertrophy in a tracing with the horizontal or semihorizontal electrocardiographic position.

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THE PATIENT WITH FUNCTIONAL CARDIOVASCULAR DISORDERS (NEUROCIRCULATORY ASTHENIA)

LIEUTENANT COLONEL WELDON J. WALKER, MEDICAL CORPS,
UNITED STATES ARMY

NEUROCIRCULATORY asthenia, a syndrome first described shortly after the Civil War by Da Costa,[1] is a disorder, the chief symptoms of which are breathlessness, palpitation, nervousness, left thoracic pain, fatigue, dyspepsia, spells of dizziness, faintness, and "anxiety attacks." The cardinal signs are those of increased activity of the sympathetic nervous system with functional disturbance of the respiratory, vasomotor, muscular, and sudomotor systems. It has been estimated as the sole disability in from 10 to 50 per cent of the patients who visit cardiologists (White and Jones[2] and Bowman[3]). The importance of its prompt recognition and proper treatment should be apparent. The symptoms of this disorder are as diffuse as the interest of the examiner and the distribution of the patient's nervous system. Cohen and associates[4] listed forty-three separate symptoms commonly encountered in this disorder. Hence, we are dealing, not with heart disease, but with persons who complain of their hearts. Only in the neuroses does the practitioner encounter such a diversity of symptoms, and only when the physician recognizes his patient as a frightened and anxious individual with the physiological manifestations of fear as described by Cannon[5] does this confusing array of symptoms make a coherent and comprehensible clinical picture. Experimental and clinical studies have indicated that these patients' complaints are real and have a physiological basis.

CLASSIFICATION

It seems most logical to consider neurocirculatory asthenia not as a specific form of neurosis, but as the physiological manifestations of anxiety which are reflected in the cardiovascular system but by no means confined to that system. In general, anxiety can produce the same manifestations in "normal" individuals. When these manifestations persist, underlying neurosis is almost invariably found. Simple anxiety reaction is the usual basis for this, but patients suffering from various other more complex neuroses may present identical cardiac manifestations of anxiety. It is desirable to classify functional cardiovascular disorders into two groups, those in which the psychological aspect of anxiety is overt and those in which it is repressed.

Anxiety Reaction With Cardiovascular Manifestations.—Most patients fall into this category. The anxiety may be diffuse and not fixed on definite situations or threats. These patients complain of nervousness, fear, or anxiety and

From the Medical Service, Gorgas Hospital, Anacon, Canal Zone.
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manifest those changes in vegetative function which occur as an integral part of their emotional state. It is the chronicity of the emotional state with its attendant changes in autonomic function that constitutes the pathological nature of this reaction and distinguishes it from normal apprehension or fear.

Somatization Reaction With Cardiovascular Manifestations.—These patients manifest all the physiological signs and symptoms of anxiety but none of its conscious psychological components. Questioning will usually uncover a past history of anxiety, and often a current, intolerable life problem which one would expect to excite anxiety. However, the patient will deny "a worry in the world." Yet to the examiner the relationship between the "heart attack" about which he complains so bitterly and certain stresses of life is most suggestive or even obvious. What are the dynamics in this more complex disorder? This patient started like the others by reacting with fear and anxiety to his particular problem, but the anxiety became intolerable to him. By some intrapsychic transfer the conflict became largely unconscious, and the anxiety was relieved by channeling the originating impulses through the autonomic nervous sytem into visceral organ symptoms and complaints. The symptoms are due to a chronic and exaggerated state of the normal physiology of the emotion, with the feeling or subjective part repressed. Such a dissociation of the mental from the physiological components of emotion has been produced experimentally by Deutsch and Kauf.[6] It was suggested to a subject under hypnosis that he would have complete amnesia for a highly charged emotional experience, yet when casually shown a handkerchief he would have the same sensations as during the experience. Following this, the mere sight of a handkerchief caused an increase of 27 beats per minute in the pulse rate without his consciousness of its emotional equivalent. Some patients manifest an incomplete transition between anxiety reaction and somatization reaction.

MANIFESTATIONS

Personality Structure.—A careful study by Wood[7] of several hundred neurocirculatory asthenia patients caused him to conclude that 94 per cent were psychoneurotic. Cohen and associates[4] subjected seventy-two patients to three different batteries of psychological tests to see whether studies which did not depend on the observer's bias would confirm the clinical impression that neurocirculatory asthenia patients belong to the group called by others "neurosis." In each of the three tests, patients obtained scores which placed them in the neurosis category. Ross[8] reported similar results with the Rorschach test. The acute cases received a less "abnormal" score than the chronic ones. Friedman[9] concluded that neurocirculatory asthenia was a variant of anxiety neurosis and could be differentiated only in that its most dramatic symptoms were referable to the cardiovascular system. That this is not a fundamental variation is indicated by the observation that some patients on successive hospital admissions have been diagnosed as having neurocirculatory asthenia on the cardiovascular service, gastric neurosis on the gastroenterological service, and anxiety neurosis on the neuropsychiatric service, simply by a slight shift in the emphasis of their complaints.

Precordial Pain.—Precordial pain often brings the patient to the cardiologist with the conviction that he has a "bad heart." The pain is of two types. The most common is a piercing, transient pain that begins in the region of the left nipple and penetrates into the depth of the chest as though the individual were being stabbed with a knife; coincidental with this pain the patient is usually conscious of "pounding" and "skipping" of the heart. Friedman[10] asked patients to report to him immediately on experiencing this type of pain. All were noted to display some form of cardiac arrhythmia or a rapid, forceful pounding of the heart against the chest wall. Except for a residual tenderness to pressure, the precordial pain did not persist after the arrhythmia or excessive pounding of the heart disappeared. This pain is aggravated when the patient lies on his left side, a position which increases the impact of the heart against the chest wall. That this is the principal causative factor is supported by the demonstration of Wood[7] that procaine infiltration of the intercostal muscles at the site of tenderness completely abolished this pain.

The other type of precordial pain is continuous, dull, poorly localized, and usually referred to the left anterior hemithorax or substernal region. Both Wood and Friedman have noted that patients with this type of pain are usually given to costal breathing, and the pain often follows tachypnea either from exercise or induced hyperventilation. Wolf[11] discussed situational conflicts with seventeen patients while they were under fluoroscopic observation. A tonic contraction of the diaphragm resulted so that a deep inspiration was no longer possible. Precordial and chest pain frequently accompanied such sustained diaphragmatic contraction. The presence of a pounding heart against the left thoracic cage probably aggravates the pain and makes the patient more conscious of discomfort in this region.

Respiratory Manifestations.—Inability to take a deep or satisfactory breath is almost a constant complaint. Irregular deep sighing respiration is often demonstrable in the curve of a basal metabolism test. Tachypnea is noted, and respiratory measurements show an increased minute volume. Wolf and Wolff[12] demonstrated a similar increase in minute volume when individuals are subjected to emotional stress. No impairment of oxygen or carbon dioxide exchange has been demonstrated. Chemical studies of the blood and urine by Wood[7] ruled out respiratory alkalosis as the principal cause of the symptoms of neurocirculatory asthenia. He also pointed out that these patients unlike normal controls do not manifest involuntary apnea after induced hyperventilation.

Basing it on the above fact, Friedman[13] described an interesting breath holding test. A normal individual is able to hold his breath longer after a 45 second period of hyperventilation than without such a preliminary period of hyperventilation. Individuals who were unable to hold their breath at least 1.3 times as long after hyperventilation were invariably found by him to be suffering from neurocirculatory asthenia or anxiety neurosis. This test is almost always positive in acute neurocirculatory asthenia. In anxiety states there seem to be nervous stimuli which prevent more than brief apnea regardless of reduced carbon dioxide content of the blood. Ability to maintain apnea after hyperventilation

often improves remarkably as anxiety decreases (Table I). This test is useful in forming a preliminary opinion as to whether a patient is suffering from neurocirculatory asthenia. A patient with organic heart disease may have symptoms due entirely to neurocirculatory asthenia.

TABLE I. MAXIMUM PERIOD OF BREATH HOLDING IN SECONDS

INTERVIEW NUMBER	BEFORE HYPERVENTILATION	AFTER HYPERVENTILATION
1	20	20
2	23	27
3	23	28
4	26	38
5	43	55
6	42	65
7	35	35
8	43	60
9	44	50
10	54	64
11	52	80
12	48	65
13	53	88
14	50	95

This table shows the improved breath holding ability of Case 2 as anxiety decreased during the course of psychotherapy. It is of interest that the relatively poor performance noted at the seventh interview followed a quarrel between the patient and her husband.

Hyperthermia.—Friedman[14] called attention to the frequent occurrence of hyperthermia in patients with neurocirculatory asthenia in whom most extensive and prolonged study failed to reveal evidence of chronic infection. Thirty-seven per cent of his patients demonstrated fever which rarely exceeded 100.4° F. He further demonstrated a temperature elevation of 0.5° to 1.5° F. when these individuals viewed an intensely gripping combat movie, as well as temperature elevation from the administration of central nervous system stimulants such as caffeine and amphetamine. These patients also showed a temperature rise of approximately 4° F. in response to a stated amount of typhoid vaccine administered intravenously, while more relaxed controls showed an elevation of about 1° F. Goodell and co-workers[15] showed that the amount and duration of elevation in body temperature in response to a given amount of work is closely related to the pre-existing emotional state. Krajazhev[16] reported a marked rise in body temperature as almost a constant finding in acute experimental neurosis in dogs. Body temperature is controlled through two centers in the hypothalamus, (1) a heat dissipation and (2) a heat maintenance mechanism. The heat maintenance mechanism is regulated by the hypothalamus through the sympathetic nervous system (Solnitzky[17]). Since the patient with neurocirculatory asthenia shows many manifestations of excess sympathetic activity, it seems likely that there is associated increased activity of the heat maintenance center.

Peripheral Sympathetic Manifestations.—Since such manifestations as tachycardia, hyperhydrosis of the hands, feet, and axillae, peripheral vasoconstriction, and dilated pupils are thought to indicate sympathetic nervous

system discharge, it becomes important in understanding the syndrome to determine whether this discharge results from unusually sensitive sympathetic nerve endings or from excessive discharge in the higher centers. That they originate in the higher centers is indicated by Friedman's[9] report that the administration of the central acting drugs, caffeine citrate (500 mg.) or amphetamine sulfate (10 mg.), caused an average increase of 16 heartbeats and 6 respirations per minute in neurocirculatory asthenia patients. The tremor of each patient was accentuated, the hands became wet and cold, and there was increased impact of the heart against the chest wall. Normal controls given the same medication showed no significant change in either force or rate of pulse and respiration. On the other hand, Wood[7] showed that these individuals do not respond unduly to peripheral-acting autonomic drugs such as epinephrine, physostigmine, or atropine. Sweating tests showed they were not hypersensitive to cholinergic drugs. While the predominant sympathetic manifestations have been emphasized, it is not intended to imply that there is a repression of parasympathetic activity. As pointed out by Langworthy,[18] the two systems are not necessarily antagonistic in function, but have different activities which often are correlated. Groedel's[19] report that the effect of emotion is still evident in the totally sympathectomized dog would indicate that the autonomic nervous system is not the sole mechanism responsible for the peripheral manifestations of emotion. The control of the pituitary gland through the hypothalamus (Best and Taylor[20]) is probably an important accessory mechanism.

Exercise Tolerance.—Impaired tolerance to physical activity is so much a characteristic of neurocirculatory asthenia that it was called effort syndrome, a poor term since the attacks occur at rest as well as during exercise. Friedman[9] found that these patients performed less strenuous forms of physical exercise as efficiently as normal individuals so long as there was no strong emotional reaction to the performance of the exercise. Stevenson and associates[21] demonstrated that similar signs and symptoms of effort intolerance occur in normal persons during periods of life stress and emotional disturbance. This intolerance may come and go repeatedly, and its presence or absence at the time of examination will depend upon the life situation of the subject and also upon the circumstances and significance of the examination. Emotionally disturbed individuals had a significantly increased cardiac output both during rest and following exercise as compared with the levels when relaxed. The effect of the emotional state on effort tolerance is illustrated in the case report by Bishop and Kimbro.[22] A man was discharged from the Army in both World Wars with objective evidence of marked effort intolerance, yet he had worked effectively as a farmer during the intervening years. In addition to the emotional effect on effort tolerance is the fact that most neurocirculatory asthenia patients have avoided strenuous activity because of the belief that their hearts were bad and consequently are in a poor state of physical condition. Cohen's[4] view that these individuals possess a defect in aerobic metabolism seems most unlikely.

Fatigue.—As pointed out by Wilbur,[23] a sense of fatigue is one of the most common complaints of the neurotic. It was a major complaint in 88 per cent

of the neurocirculatory asthenia cases studied by Wood[7] and in 91 per cent of those studied by Cohen and associates.[4] Two types of fatigue are encountered, a chronic persistent form and acute attacks of extreme weakness, tremulousness, sweating, and vertigo. The mechanism of these attacks is not clear. Alexander and Portis[24] believed both the chronic and acute forms of fatigue were explained by functional hypoglycemia. They reported excellent therapeutic results from combined psychotherapy and medical management. Weiss and English[25] have stated, "Their energy is low because it is consumed by emotional conflict and often it can be liberated by appropriate psychotherapy." The report of Hadfield[26] that exhausted soldier patients who could hardly walk, would, under hypnosis, act out with great energy terrifying incidents and afterwards be not more, but less exhausted, tends to support this view.

Cardiac Arrhythmias.—Although some workers have not found a significant increase in cardiac arrhythmias in these patients, Friedman[9] took electrocardiographic tracings at the exact time patients complained of precordial distress and found that more than one-half demonstrated some type of cardiac arrhythmia, paroxysmal tachycardia, auricular flutter, or ventricular premature contractions being most common. Stevenson and co-workers[27] studied the relationship between emotions and premature contractions by discussion of significant personal topics with patients. These authors reported that the number of premature contractions paralleled the intensity of outward manifestations of anxiety. Confirmation that arrhythmias can result from stimuli arising in the higher centers has been demonstrated in animals by inducing premature contractions through posterior hypothalamic stimulation (Beattie and associates[28]) and tachycardia by stimulating the premotor area (Grenell[29]). The importance of considering emotional factors in dealing with cardiac arrhythmias is illustrated in Case 1.

NATURE OF THE DISORDER

Medical literature frequently subdivides neurocirculatory asthenia as due to constitutional factors, fatigue, postinfection, and psychoneurosis. Such a classification is misleading if not meaningless, since essentially all who manifest the complete picture are psychoneurotic. Convalescent patients often manifest a vasomotor instability and marked effort intolerance. They will not, however, manifest the anxiety, the attacks at rest, and many other characteristics of the syndrome. Fatigue due to excess phsycical exertion is often blamed by the patient as the cause of his trouble, this being particularly true in military medicine. However, this claim by the patient is about the only evidence to support such a view. Combat experience showed a direct correlation between the number of combat casualties and psychiatric casualties, presumably due to the emotional stress of battle. However, military units which advanced against little enemy opposition showed no increase in psychiatric casualties, even though conditions were such as to produce extreme physical fatigue (Hanson[30]). It appears that fatigue may be a factor in potentiating the impact of severe emotional stress, but it does not in itself produce psychiatric casualties. It would seem valid to consider combat experience as applicable to neurocirculatory

asthenia since anxiety reactions comprised about 85 per cent of the total neurotic disorders of combat (Hanson and Ranson[31]).

Many authors have noted the familial incidence of neurocirculatory asthenia and postulated that it is an hereditary disease. This merely resumes the argument as to whether neurosis is hereditary which is brought forward recurrently by workers who seem unable to believe that psychogenic factors can produce disease. Most psychiatrists believe the familial incidence of neurosis reflects the difficulty of developing a well-integrated personality by one who is subjected to the stress and insecurity of growing up in the tension-ridden atmosphere of a neurotic environment. That emotional stress is the prime factor is supported by the experience of the last war in which it became evident that even the most normal soldier could be brought to neurotic decompensation if stress was of sufficient intensity and duration (Hanson[32]). The antecedent personality seemed to be an important factor in determining when the "break" would occur (Grinker and Spiegel[33]). The ability to produce predictable types of neuroses in experimental animals (Lindell[34]) is against an hereditary basis of neurosis. Heredity may act as a predisposing factor, but emotional stress as the precipitating factor has been demonstrated repeatedly. It, therefore, seems more rational to focus attention and efforts on factors which can be modified and in many cases alleviated rather than on those that only "providence" can alter.

Several authors have attributed cardiac neurosis to the fact that a physician "suggested" the patient had a bad heart, spent an unusual time in examining his heart, or told the patient to "take it easy." That fixation on such incidents usually results from the anxiety state and is not its cause is indicated by the reported incidence of 5.6 to 10 per cent of neurocirculatory asthenia in the general population (Wheeler and co-workers[35] and Burch and Reaser[36]), while the incidence as a complicating factor in patients with known organic heart disease is reported as 3 to 5 per cent (Craig and White[37] and Nesbit[38]). Surely the latter patients have had extensive examination and admonition by physicians relative to their cardiovascular system, yet they manifested a lower, not higher, incidence of neurocirculatory asthenia. This supports the view that prolonged emotional conflicts, not isolated "incidents," are the most important factors in producing neuroses in adults.

ROLE OF THE HYPOTHALAMUS

The hypothalamus is the principal focus of integration of the autonomic nervous system; the anterior portion contains primary parasympathetic representation, the posterior part sympathetic. The hypothalamus plays an important part in emotional expression, but it is not the seat of the emotion (Solnitzky[17]). In the distribution of the sympathetic nervous system, each preganglionic fiber bifurcates in such a way that synaptic relationship is established with many postganglionic neurons. This diffuse contact forms the anatomical basis for the widespread, massive sympathetic responses of the body. Friedman[9] called attention to the intense paroxysmal sympathetic discharge which occurs in patients with neurocirculatory asthenia and postulated that it indicated hypothalamic disease. However, Grinker[39] introduced an electrode through the nasal cavity

of humans to the immediate vicinity of the hypothalamus; this allowed him not only to record electrical impulses from the hypothalamus but to stimulate it directly by electrical means. He observed repeated prolonged bursts of excitation in the hypothalamus and noted that it did not always discharge at once in response to stimulation, but sometimes acted as a reservoir before finally discharging. The same electrical effects resulted from direct electrical stimuli as from "emotionally laden" stimuli. The author believes that the paroxysmal discharge described by Friedman represents normal, not abnormal, function of the hypothalamus. This characteristic hypothalamic discharge explains the observations of Jones and Lewis[40] that in neurocirculatory asthenia pure fear was not invariably and immediately followed by the objective physiological disturbances of the syndrome. Friedman also believed that a state of "corticohypothalamic imbalance" existed in neurocirculatory asthenia. As previously noted, those patients who manifest anxiety usually mirror the intense emotional feeling with equally intense sympathetic discharge and except for the paroxysmal nature of hypothalamic discharge show no imbalance between activity in the cortex and hypothalamus. However, in all somatization reactions in which the emotional element is repressed, such an imbalance is a characteristic feature of the disorder. Elucidation of the nature of the altered physiology in somatization reactions will contribute greatly to our understanding of the neuroses and neurophysiology.

DIFFERENTIAL DIAGNOSIS

The most important factor in correct diagnosis depends on the ability of the examiner to recognize neurosis and diagnose it by positive means. Without that ability he must rule out countless diseases. The usual patient will display not a few, but many, symptoms which no single organic leasion could explain. The symptoms are usually as wide spread as the distribution of the sympathetic nervous system. The patient demonstrates anxiety, frequently shows indecision under conditions which ordinarily would not cause it, has unexplained lapses in memory and diminution in accustomed rapidity of thinking, calculating, or planning. The history is often indefinite and rambling; the patient may break into tears without obvious reason. Usually some emotional stress preceded the illness, and often there will be a family or personal history of previous nervous breakdowns or poor social adjustment with frequent change of school or job. Since organic and functional disease may coexist, the competent physician must diagnose both on the basis of positive findings in the history and examination. If we accept the statements of Wilbur,[23] Ebaugh,[41] and Bowman[2] that between one-third and two-thirds of the patients who consult doctors do so for conditions that are largely psychogenic in origin, then no greater blame should be attached to the physician who fails to make a physical examination than to one who fails to explore the mind.

Only a few diseases will be discussed specifically in the differential diagnosis. Early valvular heart disease rarely produces symptoms and should not cause confusion.

Myocardial Infarction and Coronary Artery Disease.—Acute anxiety attacks in which the patient manifests precordial pain, tachycardia, cold sweat, physical prostration, and a sense of impending death have not infrequently been diagnosed initially as myocardial infarction. Such attacks usually have their onset at an early age while coronary artery disease is commonly encountered after the age of 40 years. Coronary disease is largely a disease of men, but neurocirculatory asthenia predominates in women. Pain in coronary disease is usually substernal; in neurocirculatory asthenia it is more commonly localized in the vicinity of the left nipple with local tenderness. Anginal attacks are of short duration, usually provoked by muscular exertion, and the patient characteristically stops until the pain ceases. The "anxiety attack" may come on while the patient is at rest and frequently leads the patient to get up and walk about and tends to be of longer duration than angina pectoris.

Thyrotoxicosis.—Patients with hyperthyroidism and neurocirculatory asthenia may have many similiar manifestations, e.g., nervousness, weakness, tremor, hyperhidrosis, tachycardia, palpitation, and a short circulation time. However, those with neurocirculatory asthenia fail to manifest thyroid enlargement and the eye signs of thyrotoxicosis and have cold hands and a normal tolerance to heat, as well as normal values for the basal metabolic rate, protein-bound iodine, and rate of radioactive iodine uptake. Moreover, they have positive evidence of anxiety neurosis.

Chronic Brucellosis.—Neurocirculatory asthenia patients with their frequent low-grade fever, multiple vague complaints, and normal erythrocyte sedimentation rate have often been suspected of suffering from chronic brucellosis. However, Agnew and Spink[12] have shown that patients with bacteriologically proved brucellosis, like those with other infectious diseases, usually have an elevated sedimentation rate. The difficulty in differentiating these two conditions should be decreased by currently more effective brucellosis therapy, a more ready recognition of the neuroses, and realization that a low-grade fever is common in neurocirculatory asthenia.

TREATMENT

General Considerations.—That psychiatric therapy had much to offer the patient with functional problems was demonstrated amply during World War II. Neurocirculatory asthenia is a neurosis which may be manifested as an anxiety neurosis or somatization reaction, the latter representing a response to or progression of the former. These conditions, in turn, are not essentially different whether the principal manifestations are referred to the cardiovascular or to some other body system. They constitute the majority of neuroses encountered in medical practice and, in general, are the ones most amenable to therapy. Because of their great numbers it is obvious that no conceivable growth of psychiatry will provide care for all these patients. Neither is it desirable. The competent practitioner must become a "minor psychiatrist" and treat the less severe cases and refer the major ones to experts in the field. The physician who does not treat these patients for their emotional disturbance is mishandling a sizable portion of his practice. The keystone of successful therapy is accurate

diagnosis. This entails not only the realization that a neurosis is present but also recognition of the specific emotional factors which precipitated it in the individual case.

Psychotherapy.—Psychotherapy is based on the principle that psychopathology arises as an end result of a logical progression of events and can be understood as these links in the chain become known. The most important single ingredient of successful psychotherapy is the attitude of the physician. He must display sincere interest, sympathy, honesty, and, most important, respect for the patient. The physician who believes the patient has his symptoms and neurosis because he is made of "second rate stuff" cannot hide this attitude for long from the patient who, in turn, becomes resentful and distrustful of the physician. Such a physician's viewpoint may change if he will make a careful assay of his antecedent emotions the next time he experiences a headache, insomnia, pounding of the heart, wet sweaty palms, or abdominal pain, especially if he has eaten when angry. After personally recognizing the relationship between one's own emotions and some of these manifestations, it is surprisingly easier to view them as the normal physiology of emotional expression.

The patient should be allowed to tell his story completely with as few interruptions as possible by the physician who takes the part of a sympathetic listener. In addition to a complete medical history, inquiry should be made for personal or family history of "nervous breakdowns" or chronic poor health. An idea of the patient's social, school, and work adjustments should be formulated. Careful assessment of the patient's interpersonal relationships must be made, e.g., rejected as a child or fear of dominating persons. Sexual and marital adjustment should be asked about. If on completion of the history and physical examination it is believed that the patient is suffering primarily from an anxiety state or somatization reaction, he is informed somewhat as follows: "Mr. Jones, after a thorough examination I find that you do not have any serious heart disease, although you have suffered from distressing chest pain and are naturally concerned about it. I believe the pounding and skipping of your heart results from a nervous reaction rather than from disease in your heart. For instance, if you walked down a dark alley at night and a masked bandit suddenly stuck a gun in your ribs, I am sure your heart would beat very fast and hard—not because it was bad, but in response to the nerve impulse that went out because of the fear you were experiencing. Your breath would also come short and fast, and your hands would be wet and shaking as they were when you came into the office. Prolonged worry, tension, anger, or anxiety can produce the same nervous impulse as intense fear. That this is probably a factor in your case is suggested by the appearance of your symptoms shortly after the arrival of the new foreman with whom you are having trouble. The pain beneath your left nipple probably results from spasm in your muscles of breathing. You are afraid that your heart is bad, and as a double check I suggest we get an electrocardiogram, chest x-ray, blood test, and urinalysis as a part of a complete medical evaluation. I expect they will be normal since no form of heart trouble can completely explain your symptoms while a tension state readily can." It is important that a positive diagnosis be made before doing the laboratory studies.

The physician shows confidence in his diagnosis, and as each normal laboratory study is reported the patient's confidence in the physician is increased. If he orders extensive laboratory studies without telling the patient he expects them to be negative, with each normal finding the patient's esteem for the physician will drop. The patient assumes the tests were ordered to find out what produces his symptoms. When the physician finally tells the patient that they are due to nervous factors, it appears he is saying this because he has been unable to find anything abnormal with the tests. To the patient it looks like an alibi, his confidence in the doctor is shaken, and the usual story is for him to consult a different physician who, too often, "does some different tests."

For a few patients who have well-integrated personalities adequate psychotherapy may consist in a careful examination and reassurance. However, almost always more is needed. The patient often harbors irrational fears arising from various manifestations of his condition. The physician must learn these fears and not only reassure the patient of their benign nature but give him a reasonable explanation of his symptoms which he can understand and accept. The next step is to learn the factors that form the basis of the emotional conflict which usually exists. The physician should keep in mind that emotional upsets result from the frustration of an individual's normal drives such as the desire to be loved, the desire to be respected by one's associates, the desire for sexual gratification, the desire for economic security, and the like. An attempt should be made to determine the individual's degree of success in achieving these both in the present and past. The latter is important since neurosis tends to be a recurring pattern. The emotional reaction may have been appropriate originally but is being persisted in as the patient's reaction to his present problem to which it may be entirely inappropriate. If advice is given at the first session, it should be very simple, such as, "Carry on in spite of fears and discomfort."

The physician's entire attitude should be concerned with understanding, not judging, the patient. He need not determine what is "right" or "wrong," "good" or "bad." It is not the physician's task to dig out confessions or to discuss sexual experiences prematurely. He should create an atmosphere of trust and confidence into which the patient will spontaneously bring his sensitive, anxiety-laden experiences, memories, and fantasies. As pointed out by Dunn,[43] these patients tend to have a severe and self-punishing conscience. Even if they are aware of a conflict, they may be unable to admit it because they are sure they will find an equally punitive attitude in the physician. Therefore, one of the early therapeutic goals is to convince the patient that the conflict responsible for his symptoms is not shameful and stigmatic. The wise physician is slow to offer advice. The problem has to be worked out with the patient's resources and by the modification of his attitudes, which may be a gradual process. Acceptance, support, and understanding are the most important contributions from the physician. Procedures which he may utilize are environmental manipulation, release of emotions, explanation, reassurance, suggestion, persuasion, desensitization, and re-education. Reassurance is more effective when offered sparingly and thoughtfully rather than frequently and glibly.

With experience the physician's ability to appraise the patient's condition will improve. His appraisal will largely determine the therapeutic goal. For the patient whose illness is of short duration or whose history indicates a prior well-integrated personality, one attempts to "work out" the problem with him which, in essence, is finding the better way to meet a life situation. Early therapy for these patients is most important so their symptoms will not become fixed. For the individual who gives a lifelong history of neurotic reactions and chronic ill health, a more modest therapeutic goal must be sought. However, such a patient can be benefited greatly by the sympathetic physician who gives him an opportunity to get some of the pent-up emotions "off his chest" as well as an emotional lift from the realization that his personal physician is a true friend to whom he can go in time of need.

Medical therapy, usually as barbiturate sedation, may be of value in relieving symptoms and giving the patient needed sleep and rest. It should be administered with the realization that it is merely a temporary symptomatic measure that does not attack the fundamental cause of the illness.

The greatest single objection to psychotherapy is the time required with the consequent increased cost to the patient. However, it should be explained to the patient or to a responsible relative that a number of office interviews are an essential part of the proper study and treatment of the emotional aspects of the patient's illness. The over-all cost in this way may be much lower than if the patient drifts along through a prolonged series of emergency calls, futile electrocardiograms, x-ray studies, metabolic tests, hospital "check-ups," and endless procedures.

A patient with coexisting neurocirculatory asthenia and organic heart disease should receive appropriate therapy for both conditions. The increased cardiac output which results from anxiety[21] may well be the extra load that causes a damaged heart to fail or become symptomatic.

Prognosis.—Wheeler and associates[14] showed that neurocirculatory asthenia does not predispose to other diseases or lead to early death. His statement that these patients do as well by receiving a careful examination and reassurance as by more extensive psychotherapy is at variance with the opinions of experienced psychiatrists (Rennie[45] and Whitehorn[46]). In the author's opinion, the figures quoted were hardly comparable and could be used just as well to draw an opposite conclusion.

More effective screening of chronic neuroses at induction stations during World War II eliminated some of the more difficult psychiatric problems and must be considered in comparing therapeutic results in the two wars.

However, the possible results from early and proper psychotherapy in acute neurosis (largely anxiety reactions) are illustrated by the results reported from our Seventh Army during its European operations (Hanson and Ranson[31]). In seven of eleven divisions, between 70 and 89 per cent of the psychiatric casualties were returned to full combat duty. Follow-up studies to determine their effectiveness showed there was no essential difference in those returned to combat after hospitalization for sickness, minor injury, or neuropsychiatric disorders. A further follow-up study of 358 patients who were evacuated from the Seventh

Army Neuropsychiatric Center showed that 310 (86.6 per cent) of these individuals were reassigned to noncombat duties. A follow-up on these 310 patients showed that their commanding officers rated the performance of their new duties as satisfactory or better in 93 per cent of the cases, a considerable improvement from the results of World War I where 20 per cent were returned to full duty (Lewis[47]). The principal change in therapy was early treatment of the patient's emotional problems rather than the organ system of which he complained.

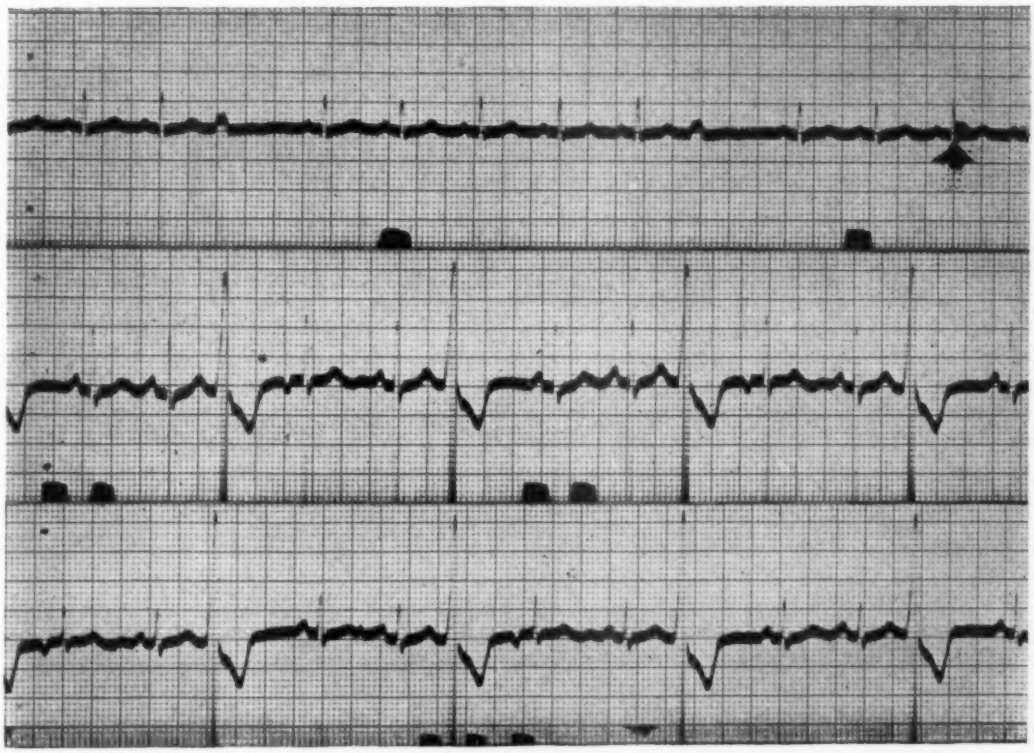

Fig. 1.—Electrocardiogram of May 22, 1950. The tracing shows numerous ventricular premature contractions from a single focus. Wandering supraventricular pacemaker is evidenced by the variable configuration of P waves which is most evident in Leads II and III. Only the standard limb leads are shown.

CASE REPORTS

CASE 1.—A 47-year-old, married, white woman complained of fatigue, skipping and pounding of the heart, recurrent pain in the region of the left nipple, slight afternoon swelling of the ankles, and dizzy spells. The onset of symptoms had been noted about nine months before and had become progressively more disturbing, but had not prevented her from doing her work as a secretary. On three occasions during this period the patient had been thoroughly examined by physicians who had found a persistent cardiac arrhythmia but had reassured her that she did not have serious cardiovascular disease. This reassurance plus barbiturate sedation had failed to improve her cardiac arrhythmia or remove her symptoms. She presented an electrocardiogram which had been taken ten days previously. This showed many ventricular premature contractions arising from a single focus and a wandering supraventricular pacemaker (Fig. 1). She had no orthopnea, cough, or nocturnal dyspnea. The patient had enjoyed good health previously,

with no history of nervousness or emotional disturbances. Menses were regular every twenty-six days and lasted four days. Because the symptoms suggested an anxiety state, the patient was carefully questioned in regard to marital, emotional, and economic problems. She manifested a warm and responsive personality and appeared to make a sincere effort to answer all questions completely and honestly. She convincingly denied nervousness, worry, marital discord, or other emotional problems. She related having enjoyed very satisfactory sexual relations during twenty years of married life. However, for the past several months she had practically lost sexual desire and had been able to achieve orgasm but once. This again pointed to a functional disorder but gave no clue as to its cause. There had been no change of residence, employment, or interpersonal relations in the immediate family that coincided with the onset of the patient's complaints.

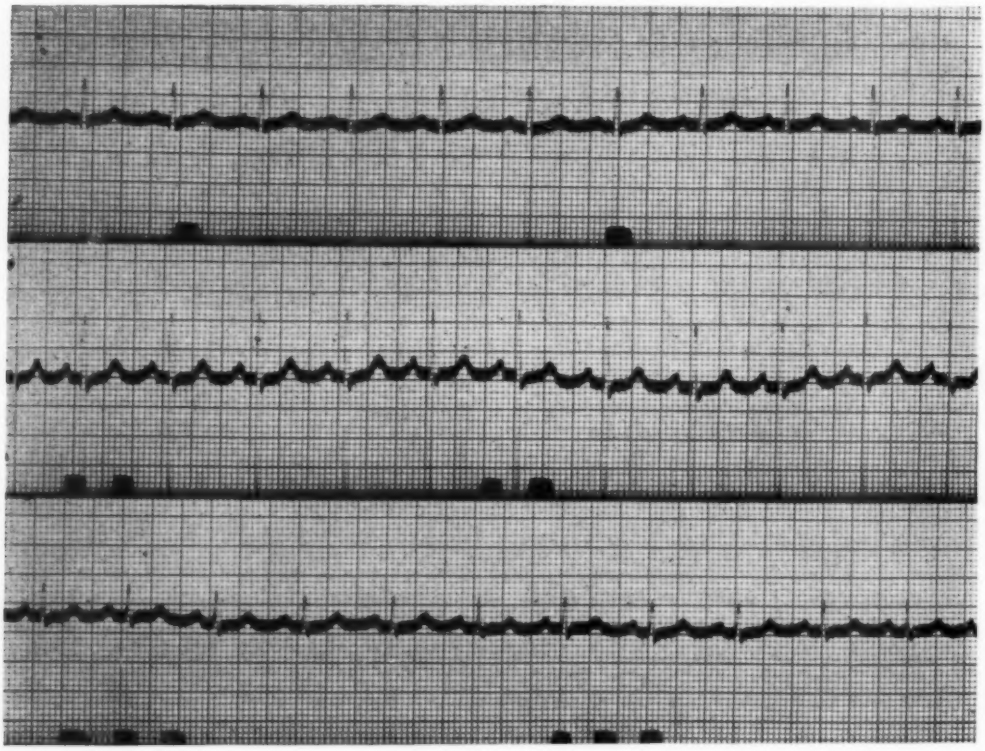

Fig. 2.—Electrocardiogram of June 14, 1950. The tracing shows normal sinus rhythm. Only the standard limb leads are shown.

Physical examination was normal except that the blood pressure was 150/90 mm. Hg and the cardiac rate was 106 per minute with numerous ventricular premature contractions which at times produced bigeminy. There was no evidence of congestive failure. The heart was not enlarged, and the arm-to-tongue circulation time (calcium gluconate) was 12 seconds.

On completion of the examination the patient was asked, "Did anyone close to you die recently from heart disease?"

"Yes, my brother died of a heart attack about nine months ago, but I don't see what that could have to do with my trouble for I have hardly thought about it for several months," she replied without display of emotion.

"Tell me about your brother and his death."

Tears came into her eyes, and between sobs she related that her older brother had been both a father and brother to her following the separation of her parents when she was a child. She had

depended on his advice in her important decisions of life and had been very close to him. On the day she received a cablegram of his sudden death a long air-mail letter had arrived telling her what an enjoyable vacation he was having. The shock of his unexpected death caused her to collapse. She was unable to cry for more than twenty-four hours; she couldn't eat and avoided talking to anyone about his death. She decided against flying to the United States to attend her brother's funeral. During the ensuing nine months she had tried to forget about his death and according to herself and friends had not appeared depressed. However, it was evident she had never emotionally worked through and faced the reality of her brother's demise.

It was explained to the patient that her symptoms probably resulted from the "bottled up" grief that she had never adequately released and perhaps the suppressed fear that the skipping of her heart forecast the same fate for her that befell her brother. She was assured that the examiner did not believe that she had serious heart disease but would do further laboratory and x-ray studies to doubly reassure her. She was urged to go home and talk to her family and relatives about her brother and his death, to cry if she felt like it, and to return in two weeks.

On her return she stated "I'm almost ashamed to admit it, but guess I am well. My cardiogram will be all right today (Fig. 2). I haven't had any 'skipping' since the day after I was here. Until I started talking to the folks about him, I never realized how close my brother really was to me and how much I had to get off my chest about him."

The patient returned for a follow-up six weeks later at which time she was still free of symptoms and an electrocardiogram showed normal sinus rhythm.

Discussion.—This patient presented a clear-cut somatization reaction with many of the physiological, but few of the psychological, aspects of anxiety. A previous well-integrated personality enabled her to resolve her emotional problem almost as soon as it was recognized as the cause of the cardiac irregularity which frightened her. This case suggests that it is as important to find the specific emotional factor in dealing with functional disease as to identify the causative organism of bacterial disease. To attempt to treat such patients simply by careful examination and reassurance is similar to treating all cases of fever with quinine. This patient was not benefited by such therapy because she was well aware that she had a disorderly action of the heart that had recently appeared which not only caused her precordial discomfort but apprehension as to what its presence might portend. To explain that it was due to her "nerves" did not satisfy her since she was not consciously aware of any nervousness, and even if she were it would not have offered her much help. When she recognized her symptoms as normal physiological manifestations of intense emotion which had been repressed, she lost her fear of these symptoms and was soon able to express her emotions more directly with resulting disappearance of symptoms. The case is similar to many of the acute combat neuroses encountered in World War II which usually responded to brief psychotherapy of the type which the general physician should be able to give.

CASE 2.—A 22-year-old, married white woman was seen for an opinion concerning the presence of acute rheumatic fever. She complained of migratory pains in her bones and joints, pounding of the heart with recurrent precordial pain, difficult breathing, nervousness, and chronic exhaustion of three months' duration. She had been found to have a resting pulse rate of 100 which dropped to 70 per minute when asleep and an occasional "fever" of 99° F.

Electrocardiograms, chest and joint roentgenograms, sedimentation rate, blood agglutinations, cultures, and antistreptolysin titer were normal. Vital capacity was 3,200 c.c., and arm-to-tongue circulation time (Decholin) was 13 seconds. Basal metabolism was −2. Examination revealed that she was apprehensive and had dilated pupils and a slight tremor of her moist hands. Tears came to her eyes when asked, "Are you unhappy?" The patient could hold her breath for 20

seconds, and following 45 seconds of hyperventilation, the maximum period of breathholding was still 20 seconds. Hyperventilation caused her to complain of severe precordial pain. The joints did not show swelling, redness, or localized heat. An apical systolic click and slightly hyperactive reflexes were the only additional positive findings. She had experienced a similar illness two years before when having difficulty in college and thought she had never completely recovered. Prolonged hospital study at that time had failed to confirm rheumatic fever. Her present symptoms became acute shortly after her marriage to an intern and move to a distant land where she found herself in a crowded apartment, surrounded by noisy neighbors whom she considered unfriendly, rude, and uncouth. Her husband spent most of his time at the hospital, while she stayed at home, made no friends, and felt lonely and rejected.

The patient was told she did not have serious heart disease, that her symptoms while very real and distressing could be caused entirely by emotional tension, and that further discussion and study of her emotional problems would probably enable her to understand and deal with them more satisfactorily. She consented to this and returned semiweekly, then weekly, for a total of fourteen interviews. These revealed a lifelong history of personal insecurity in spite of economic affluence and graduation from an exclusive college. She experienced insomnia and relationships with her husband revealed the same fear and insecurity that had been her response to a demanding father. When the patient was a child, her mother had had a "nervous breakdown" which lasted for several years and was followed by semi-invalidism with headaches, "sick spells," and chronic exhaustion. Illness seemed to have been the mother's principal defense against the aggressive, driving, rigid, and demanding father. Each member of the family seemed to have striven and competed for love in his own particular way, while all had been largely incapable of bestowing affection. During treatment the patient gradually released many emotionally charged feelings, the existence of which was denied at the first interview. She recognized many of her reaction patterns as inappropriate to the present situation and began to deal with her husband on a more give and take basis. During the course of therapy she reported her first sexual orgasm. New friends and interests were cultivated, and by the eleventh interview her physical complaints had disappeared. When discharged she still showed some immature emotional reactions but was free from anxiety and had acquired the ability to face adequately most of her problems with intelligence and confidence. Interestingly, she could then hold her breath more than four times as long after hyperventilation as at the start of therapy. There had been no associated physical reconditioning or any suggestion that she was expected to show an improvement in breathholding ability. No comment either favorable or otherwise was ever made as to her breathholding performance nor were the results revealed to her (Table I).

Discussion.—This patient had manifested a chronic anxiety reaction of varying intensity for several years; she had a poorly integrated underlying personality structure and manifested rather severe chronic neurotic traits. She could probably have been handled more effectively by a skilled psychiatrist. Her case report is included because she manifested a rather characteristic picture of what is usually called neurocirculatory asthenia. She illustrates what will often be found and may be accomplished by the interested internist who looks behind the patient's presenting complaints.

SUMMARY AND CONCLUSIONS

1. The syndrome called neurocirculatory asthenia and the mechanisms of its altered physiology are reviewed.

2. The opinion is expressed that all its manifestations can be explained as the normal physiological response to anxiety.

3. Two case reports are included. One is that of a patient manifesting persistent ventricular premature contractions and a wandering supraventricular

pacemaker for nine months who reverted to normal sinus rhythm after the emotional release and insight which were achieved from a single interview.

4. The proper handling of functional cases involves learning and dealing with the specific emotional problem of the individual patient, not simply examination and reassurance of the patient that no serious organic disease exists.

5. The importance of emotional factors in causing cardiac arrhythmias is emphasized.

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PROCAINE AMIDE: ITS EFFECT ON AURICULAR ARRHYTHMIAS

ABRAHAM I. SCHAFFER, M.D., SERGE BLUMENFELD, M.D., ERNEST R. PITMAN, M.D., AND J. HARLAN DIX, M.D.

NEW YORK, N. Y.

RECENTLY, one of us participated in an investigation of the effects of procaine hydrochloride on cardiac arrhythmias when given intravenously to the unanesthetized patient.[1] It was noted that the drug had a depressant effect on ectopic stimulus formation and that it occasionally induced auricular or ventricular extrasystoles. It was also noted that it sometimes increased the ventricular rate in cases of auricular flutter and fibrillation. The therapeutic shortcomings of intravenous procaine were thought to be due in the main to its rapid inactivation in the blood by an esterase, preventing an effective concentration from being established.

A derivative of procaine, procaine amide,* has been developed which retains the quinidine-like effect, but is not so rapidly inactivated. Mark and associates,[2] who developed procaine amide, reported that it was effective in the treatment of ventricular tachycardia and ventricular extrasystoles. They noted some depressant effect on the size and rate of the F waves of auricular flutter and fibrillation, but they were unable to convert any of their patients to sinus rhythm.

METHOD

Procaine amide hydrochloride was supplied in 10 c.c. vials each containing 1 Gm. of the drug. Each vial was diluted with 20 c.c. of saline solution and injected intravenously. Blood pressure readings were taken every minute during the injection. If the pressure fell distinctly, the injection was stopped until the pressure was stabilized or began to rise, and then the injection was resumed at a slower rate. Before, during, and after the injection, an electrocardiogram was taken with a direct-writing apparatus. The lead showing the best auricular activity, usually V_1, was used. If the tracing showed either marked widening of the QRS complex or alarming arrhythmias, the injection was stopped. It was intended that the injection time should range from five to seven minutes and that a total of 1 Gm. be given in each case, but because of marked hypotensive effects, electrocardiographic changes, and mechanical difficulties, the dosage ranged from 0.25 Gm. to 1.0 Gm. and the time of injection from four to sixteen minutes (see Table I).

From the Medical Department, New York Medical College, Metropolitan Hospital Division, New York.

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*Pronestyl, a brand of procaine amide, was supplied by E. R. Squibb & Sons, New York, N. Y.

TABLE I.

CASE NO.	AGE	SEX	DIAGNOSIS	RHYTHM BEFORE THERAPY	THERAPY	RHYTHM AFTER THERAPY	REMARKS
1	56	M	Hip fracture, arteriosclerosis, generalized, moderate, right bundle branch block	Auricular extrasystoles	1.0 Gm. in 7 min. i.v.	Extrasystoles suppressed for several hours	Transient slurring of QRS and increase of Q-T during i.v. injection
				Auricular extrasystoles	2.0 Gm. in 24 hr. oral	Extrasystoles suppressed	Recurrence of extrasystoles in 2 days in spite of continued dosage
2	75	F	Old myocardial infarct, congestive failure, digitalis toxicity	Auricular tachycardia, 2:1 Carotid pressure without effect	400 mg. in 11 min. i.v.	10 min. after i.v. injection carotid pressure induced sinus rhythm	Mild hypotensive reaction; ventricular extrasystoles noted before conversion occurred; transient increase of ventricular rate
				Auricular tachycardia, 2:1	4.0 Gm. in 48 hr. oral	Sinus rhythm, auricular and ventricular extrasystoles	
				Auricular tachycardia, 2:1	0.25 Gm. in 10 min. i.v.	12 hr. later, sinus rhythm	Conversion probably spontaneous because of decreased digitalis effect
3	45	M	Pneumonectomy for tuberculosis	Auricular flutter, 2:1	3 Gm. in 24 hr. oral	Sinus	Dosage discontinued after sinus rhythm developed
				Auricular fibrillation for 7 days	7.0 Gm. in 36 hr. oral	Sinus	Began fibrillating on therapy; died 3 days later
4	71	M	Arteriosclerosis, generalized, marked	Auricular fibrillation	1.0 Gm. in 6 min. i.v.	Auricular flutter	QRS and Q-T temporarily prolonged
				Auricular flutter	4.0 Gm. in 48 hr. oral	Sinus	Persisted 10 days on this dosage
				Sinus	3.0 Gm. in 72 hr. oral	Auricular flutter	Flutter followed decreased dose
				Auricular flutter	4.0 Gm. in 48 hr. oral	Sinus	

5	75	F	Diabetes mellitus, coronary sclerosis, hypertension, pulmonary infarction	Auricular fibrillation	0.83 Gm. in 16 min. i.v.	Auricular fibrillation	Transient widening of QRS
				Auricular fibrillation 2 wk. after i.v.	3.0 Gm. in 24 hr. oral	Sinus	Endocardial injury pattern present at this time
				Sinus	1.5 Gm. in 24 hr. oral	Auricular fibrillation	Endocardial injury pattern persists
				Auricular fibrillation	3.0 Gm. in 24 hr. oral	Sinus	Reverted to fibrillation next day and died suddenly; autopsy performed
6	80	F	Arteriosclerosis, generalized, marked	Auricular fibrillation	14 Gm. in 4 days oral	Auricular flutter	Varying ventricular conduction defect present on control persists; ventricular rate 110
				Auricular flutter	4.0 Gm. in 1 day oral	Sinus	Rate 94; conduction defect persists
				Sinus	6.0 Gm. in 2 days oral	Sinus	Rate 70; conduction defect now absent
7	78	M	Cachexia, arteriosclerosis, pulmonary infarction, pulmonary edema, cirrhosis, nephrosclerosis	Auricular fibrillation	3.0 Gm. in 1 day oral	Sinus	
				Sinus	None for 2 days	Auricular fibrillation	
				Auricular fibrillation	3.0 Gm. in 1 day oral	Auricular fibrillation	Died; autopsy done
8	76	M	Syphilis, hypertension	Auricular fibrillation	46.0 Gm. in 13 days oral	Auricular fibrillation	i.v. therapy was given during the period of oral therapy
				Auricular fibrillation	1.0 Gm. in 15 min. i.v.	Auricular fibrillation	
				Auricular fibrillation	20.0 Gm. in 4 days oral	Auricular fibrillation	

(*Table continued on next page.*)

TABLE I.—CONT'D

CASE NO.	AGE	SEX	DIAGNOSIS	RHYTHM BEFORE THERAPY	THERAPY	RHYTHM AFTER THERAPY	REMARKS
9	67	M	Arteriosclerosis, generalized, marked	Auricular fibrillation	1.0 Gm. in 4 min. i.v.	Flutter-fibrillation	Runs of ventricular extrasystoles; severe hypotensive reaction
				Auricluar fibrillation	22.0 Gm. in 9 days oral	Auricular fibrillation	1.0 Gm. 3 times a day caused headache, nausea, vomiting, and diarrhea
10	76	F	Hip fracture	Auricular fibrillation	60.0 Gm. in 16 days oral	Auricular fibrillation	Increased frequency of ventricular extrasystoles; after 5 Gm. 3 times a day nausea and vomiting
11	35	F	Rheumatic heart disease with mitral stenosis and severe congestive failure, digitalis toxicity	Auricular fibrillation, complete A-V block	18.0 Gm. in 6 days oral	Auricular fibrillation	Vomited before and during therapy; little medication retained; died
12	62	M	Arteriosclerosis, coronary sclerosis, hemiplegia	Auricular fibrillation	38.0 Gm. in 12 days oral	Auricular fibrillation	
13	65	M	Arteriosclerosis, generalized, moderate	Auricular fibrillation	1.0 Gm. in 5 min. i.v.	Auricular fibrillation	Ventricular extrasystoles temporarily suppressed; QRS slurred and Q-T increased temporarily
14	60	F	Hypertension, arteriosclerosis, generalized, moderate	Auricular fibrillation	1.0 Gm. in 5 min. i.v.	Auricular fibrillation	

The oral medication was supplied in capsules containing 0.25 Gm. of procaine amide hydrochloride. It was given in amounts from 1 to 5 Gm. daily in three or four divided doses.

Of the fourteen patients treated, eleven were diagnosed as having chronic auricular fibrillation, though the exact duration was unknown. One patient showed paroxysmal auricular tachycardia due to excessive digitalis therapy. One patient showed auricular flutter following a pneumonectomy for tuberculosis. This patient also developed auricular fibrillation later. There was one case of persistent frequent auricular extrasystoles. Two patients received only intravenous therapy, six only oral therapy, and six both types of therapy.

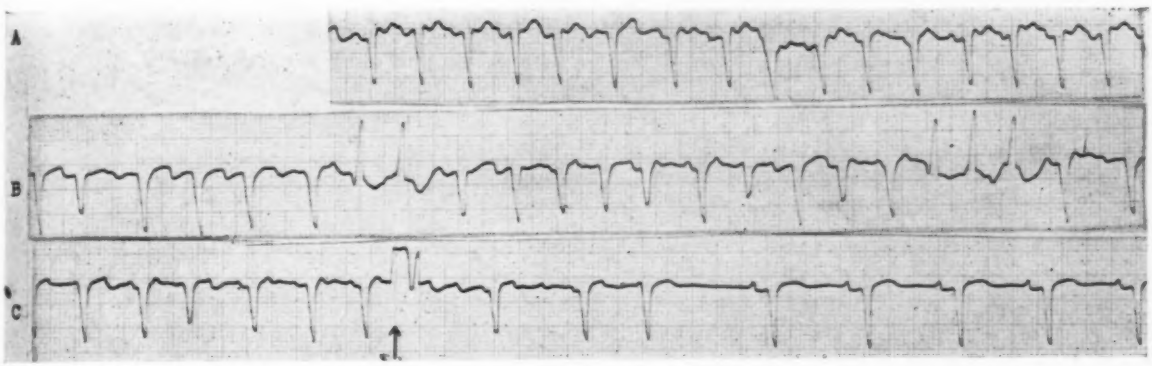

Fig. 1 (Case 2).—Auricular tachycardia due to excessive digitalis therapy. *A*, Lead V_1 recorded immediately before the intravenous injection of 400 mg. of procaine amide in eleven minutes. The auricular rate was 312, the ventricular rate 144. *B*, Lead V_1 recorded ten minutes after the injection of the drug was started. The auricular rate was 266, the ventricular rate 154. Note the runs of ventricular extrasystoles, also slurring of the QRS complex. *C*, Lead V_1 recorded ten minutes after the injection was completed. The standardization marks the onset of carotid pressure. Note the conversion to sinus rhythm.

RESULTS

Case 1 had exhibited frequent auricular extrasystoles for at least two weeks, and right bundle branch block was present. An intravenous injection of 600 mg. of procaine amide in five minutes abolished the extrasystoles for several hours. Oral administration of procaine amide was also successful in abolishing the extrasystoles, though after two days they recurred in spite of maintained oral therapy.

One patient each with paroxysmal auricular tachycardia and flutter was converted to sinus rhythm. In Case 2, with auricular tachycardia and 2:1 ventricular response, the arrhythmia was apparently caused by excessive administration of digitalis. Carotid pressure applied ten minutes after an intravenous injection of procaine amide was followed by sinus rhythm (Fig. 1). Carotid sinus pressure applied immediately prior to the injection had had no effect. Upon a recurrence of the tachycardia, oral administration of procaine amide successfully abolished it. During a subsequent recurrence of the paroxysmal tachycardia, another intravenous injection was not successful; the next day, sinus rhythm appeared and persisted, due probably to the wearing off of the digitalis toxicity.

Case 3 showed a paroxysmal flutter three days after pneumonectomy. Sinus rhythm was restored by 3 Gm. of procaine amide orally in twenty four hours. Several days later auricular fibrillation appeared. It lasted about a week, when after 7.0 Gm. of procaine amide in thirty-six hours it changed to sinus rhythm. The next day fibrillation recurred in spite of continued therapy and persisted for the remaining three days of life.

Of the six patients with fibrillation who received the drug intravenously, none were converted to sinus rhythm during or immediately after the injection. However, in two cases there was a distinct, immediate effect on the F waves. In Case 4, during the injection, the fibrillation changed to flutter that persisted for two days without additional medication. After this period the flutter was converted to sinus rhythm by oral therapy (Fig. 2). In Case 9, the injection caused a transient diminution of height and slowing of the F waves during administration.

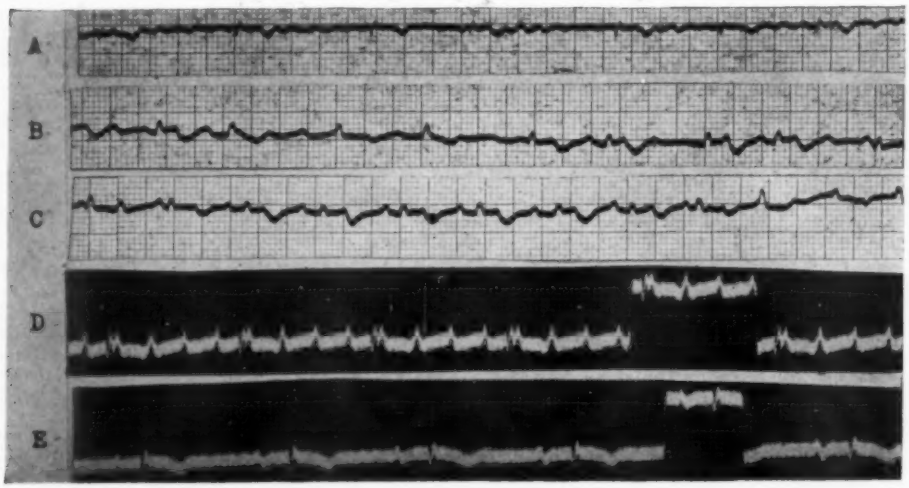

Fig. 2 (Case 4).—Auricular fibrillation converted to sinus rhythm with an intervening period of auricular flutter. All leads are V_1. *A*, Recorded just before 1.0 Gm. of procaine amide was injected intravenously in five minutes. *B*, Recorded when 600 mg. had been injected in four minutes. Note that the fibrillation has changed to flutter-fibrillation. *C*, Recorded when 1.0 Gm. had been injected in five minutes. Note the slightly impure auricular flutter. *D*, Recorded the following day. Note the accentuation of the flutter waves. *E*, Recorded after the oral administration of 4.0 Gm. in forty-eight hours. Sinus rhythm is present.

There were thirteen oral courses of procaine amide given in ten cases of fibrillation. In five cases there was successful restoration of sinus rhythm. Flutter was noted in two cases during the conversion from fibrillation to sinus rhythm. In Case 4 (Fig. 2) this occurred during the intravenous injection and in Case 6 during oral therapy.

Two patients showed an increased ventricular rate which may have been due to depression of the vagus (Case 2, Fig. 1; Case 9, Fig. 3). In both it was transient and occurred during the injection.

In three cases procaine amide appeared to induce ventricular extrasystoles. In Case 2 (Fig. 1) and Case 9 (Fig. 3) this occurred during intravenous therapy; in Case 10 this appeared during oral therapy.

In five of the eight patients who received an intravenous injection there was a distinct slurring and widening of the QRS complex during the course of the injection. Case 6 showed fibrillation and a varying intraventricular conduction disturbance in the control tracing. The latter persisted for several days after conversion to sinus rhythm with oral therapy. Then the intraventricular conduction time became more normal and showed no variation from beat to beat. This coincided with a marked decrease of the ventricular rate.

Following three of eight intravenous injections, the blood pressure showed a distinct drop. Due to an error in technique, Case 9 received 1.0 Gm. intravenously in four minutes. The pressure fell to unmeasurable levels. It began to rise within fifteen minutes and returned to the control level within one hour. Except for slight mental confusion for a few minutes, there were no noticeable clinical effects.

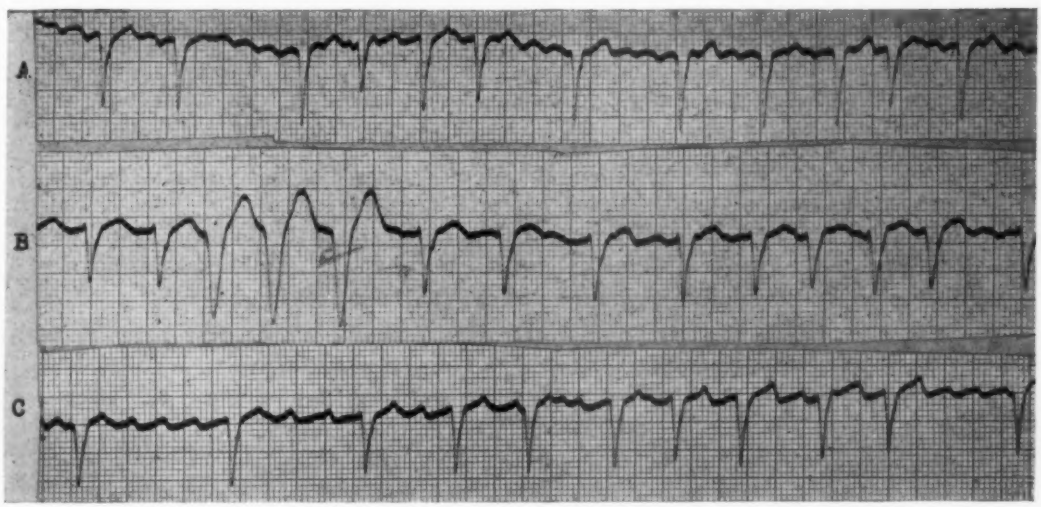

Fig. 3 (Case 9).—Auricular fibrillation. All leads are V_1. *A*, Recorded immediately preceding the intravenous injection of 1.0 Gm. of procaine amide intravenously in four minutes. Note the well-marked F waves. *B*, Recorded at the time of completion of the injection. Note the disappearance of the F waves, the increase of the ventricular rate, and the induction of ventricular extrasystoles. *C*, Recorded one hour later. Note the reappearance of the F waves in a flutter-fibrillation form.

In two cases, oral therapy caused toxic symptoms which forced the discontinuation of therapy. Case 9 received 22.0 Gm. in nine days. During the last four days the dose was increased to 1 Gm. three times a day. The patient developed nausea, vomiting, diarrhea, and headache. Case 10 received 60.0 Gm. in sixteen days. In the last three days she was given 1.25 Gm. four times daily. She developed nausea and vomiting and refused further therapy.

Four patients died while on procaine amide therapy by mouth. In three of these, death was expected and could not be connected with the therapy in question. Case 3 had a wound dehiscence following a pneumonectomy for widespread tuberculosis. Case 7 appeared near death at the onset of therapy. Autopsy showed cirrhosis of the liver, nephrosclerosis, pulmonary infarction, and edema. Case 11 had rheumatic heart disease and was admitted in terminal

congestive heart failure. Case 5 died suddenly while on procaine amide, 1.0 Gm. three times daily. It is possible that conversion to sinus rhythm may have caused a pulmonary embolus and death, but there was no evidence of toxicity to procaine amide.

DISCUSSION

The results indicate that procaine amide is clinically effective in the treatment of auricular arrhythmias.

A problem not satisfactorily solved is the one of dosage. The animal experiments of Newman and Clark[3] indicate that procaine amide is approximately one-quarter as strong as quinidine in prolonging the refractory period of auricular muscle.* The maximum tolerated single dose in the present series was 1.25 Gm. four times daily by mouth. This corresponds to 0.3 Gm. of quinidine four times daily. Quinidine in this dosage is effective in some cases of fibrillation, but in many others considerably more is necessary. Therefore, it is logical to expect even better results than already obtained here if the dosage of procaine amide could be increased substantially. Both our cases of intolerance to the drug exhibited as the chief symptoms nausea and vomiting. It is possible that this is a local gastric effect. Perhaps the total dose may be increased by the addition of one or more intravenous injections.

The induction of extrasystoles by procaine amide was not unexpected. A similar effect had been noted when the parent drug, procaine hydrochloride, was administered intravenously.[1] It is well known that quinidine may have a similar effect and also produce changes in the QRS complex.

When an idiosyncrasy to quinidine exists, procaine amide may be a useful substitute. One of us[5] has found that 0.25 Gm. of procaine amide is equivalent to 0.065 Gm. of quinidine sulfate when treating patients with auricular or ventricular arrhythmias. Newman and Clark[3] in their animal experiments also arrived at a ratio of 4 of procaine amide to 1 of quinidine.

CONCLUSIONS

1. Procaine amide has a depressant action on auricular abnormal stimulus formation. It would appear to be clinically effective in the treatment of auricular extrasystoles, tachycardia, flutter, and fibrillation.

2. Its value is limited by a tendency to cause nausea and vomiting when given orally in doses that are below the desirable range.

3. In addition to its depressant action on abnormal auricular stimulus formation, there was also noticed a tendency to induce ventricular extrasystoles, an atropine-like action, and a depressant influence on normal conduction.

The authors are indebted to Dr. David Scherf for his generous assistance and guidance.

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*We do not wish to infer that the prolongation of the refractory period is the main factor in the action of antifibrillatory drugs. According to the old concept of circus movement as the basis for flutter and fibrillation, prolongation of the refractory period would have been of prime importance in the interruption of the arrhythmia. As originally demonstrated by Scherf and associates,[4] auricular flutter and fibrillation are best considered as originating in ectopic foci.

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EFFECTS OF DIETARY CHOLESTEROL AND BILE SALT IN THE GOLDEN HAMSTER

W. MARX, PH.D., L. MARX, PH.D., AND H. J. DEUEL, JR., PH.D.

LOS ANGELES, CALIF.

IT WAS established by a great number of investigators that a diet high in cholesterol causes the development of atheromas in rabbits and chickens, but that in most other species so far investigated, such as the dog, cat, rat, and mouse, no atheromatosis is produced by cholesterol feeding.[1] In recent years another small rodent has become available for experimental work, i.e., the golden hamster, and the present work was undertaken in order to investigate how this species would respond to a high cholesterol diet.

After the experimental work reported below had been completed, two publications appeared dealing also with the effects of cholesterol feeding in hamsters.[2,3] Since the results of these two groups of investigators are somewhat at variance, the findings of the present authors will be reported briefly.

METHODS

The hamsters were first bought from local dealers, but in later experiments a more vigorous strain was obtained by breeding a few animals generously supplied by Dr. H. A. Mattill of the State University of Iowa. The age of the experimental animals varied somewhat; usually young adult hamsters were used.

The hamsters were fed ad libitum a diet consisting of one part of this laboratory's stock diet for rats,* one part of Sherman diet, and one part of rolled oats, supplemented by lettuce twice weekly. For the experimental groups, cholesterol† was added to the diet at a level of 1 per cent; the sterol was dissolved in hot cottonseed oil, and the warm solution mixed thoroughly with the other components of the diet. For one of the experimental groups, bile salt‡ was mixed with the food at a level of 0.25 per cent in order to increase cholesterol absorption.[4]

From the Department of Biochemistry and Nutrition, School of Medicine, and the Laboratories of the Allan Hancock Foundation, University of Southern California, Los Angeles.

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Received for publication Feb. 9, 1951.

*Stock diet for rats: 34 per cent whole-wheat flour, 34 per cent oats, 15 per cent skim milk powder, 4 per cent alfalfa meal, 2 per cent yeast (strain G), 8 per cent cottonseed oil, 2 per cent fortified oil containing 300 I.U. of vitamin A and 50 I.U. of vitamin D per Gm., 0.5 per cent NaCl, 0.5 per cent $CaCO_3$.

†A part of the cholesterol was supplied by F. Fenger, The Armour Laboratories, and N. F. Payton, Suburban Chemical Co., Chicago, Ill.

‡Dried extract of ox bile (U.S.P.), in part supplied by F. Fenger, The Armour Laboratories, Chicago, Ill.

After completion of the feeding period, the animals were autopsied (Nembutal anesthesia). Blood was taken from the vena cava or by heart puncture, and liver, kidneys, adrenals, and, in some instances, spleen, lungs, and brain were excised for determination of cholesterol. The aorta was taken for histological examination.

Total cholesterol was determined as described by Nieft and Deuel.[5] Plasma was prepared from heparinized blood and extracted at room temperature by adding 14 volumes of a 1:1 mixture of alcohol/acetone. Tissues were extracted with the same mixture, either using a Goldfisch apparatus* for continuous extraction or, after grinding the tissue in a mortar to a pulp (no sand added), by direct extraction in a volumetric flask provided with a reflux condenser and heated to boiling for about ten minutes. The latter procedure, which yielded better recoveries and was simpler and faster, was used in all later experiments.

For histological examination, the aorta was fixed in Formalin, and strips, especially of the ascending portion and the convexity of the arc, were embedded in gelatin and studied on frozen sections stained with Nile blue sulfate. Cholesterol was identified by its birefringence and solubility in chloroform. Interesting specimens were also examined by other methods.†

RESULTS

The general condition of the hamsters was variable. As a consequence of the feeding of cholesterol, the livers were very much increased in size and had the pale yellowish color typical of extreme fatty degeneration. Supplementation with both cholesterol and bile salt enhanced this effect, but did not seem to cause any other serious symptoms.

The results are shown in Table I. The plasma cholesterol was significantly increased in the group fed cholesterol. Addition of bile salt to the high cholesterol diet produced a further rise in the sterol content of the plasma.

In the liver, extremely high concentrations of cholesterol were found, in particular in the group fed both cholesterol and bile salt, individual animals showing values up to 12 per cent cholesterol. As the mean total liver weight was approximately doubled in these animals, the extent of the accumulation of cholesterol in the liver was quite remarkable. Even in the group fed cholesterol without bile salt, the liver cholesterol was increased approximately twenty times as compared with the control group. A slight sex difference was observed in the liver cholesterol values, the male hamsters showing a somewhat greater accumulation of cholesterol.

The gross appearance of the aortas was normal in both control and experimental animals. On histological examination, no fat drops were seen in untreated hamsters after staining with Nile blue sulfate. The most striking effect of the experimental diet was a fatty imbibition which was pronounced in four of the animals. The endothelium was loaded with fat and included foam cells.

*Laboratory Construction Co., Kansas City, Mo.

†The authors are much obliged to Dr. R. B. Barden and the Department of Anatomy of the School of Medicine, University of Southern California, for preparing and interpreting some of the initial sections and for the loan of two microtomes.

The foam cells in the hamster were peculiar in that they often carried a few minute, birefringent particles between the fat droplets. The demarcation of the particles was so definite that they were visible without polaroid lenses. The inner surface of the aorta and several rows of elastic lamellas in the medial coat had a fatty lining consisting of a thin film of extracellular fat with a high affinity for the red form of the dye. Only traces of cholesterol occurred in the endothelium and media. Structural changes were limited to the inward bulging of endothelial cells. Two animals only had small foci of hyperplastic endothelium,* while in four others, a slight uniform thickening was observed in the proximal portion of the intimal coat. A similar slight thickening was noted in the proximal intima of two of nine controls.

TABLE I. EFFECTS OF DIETARY CHOLESTEROL AND BILE SALT IN THE HAMSTER, RAT, RABBIT, AND CHICKEN

SPECIES	DIET*	FEEDING PERIOD (WEEKS)	NO. ANIMALS	MEAN CHOLESTEROL CONTENT	
				PLASMA (MG. PER 100 ML.)	LIVER (%)
Hamster	C + B	16–25	13	282 ± 34	8.68 ± 0.88
	C	25	6	160 ± 14	5.11 ± 0.17
	N		9	57 ± 5	0.22 ± 0.04
Rat	C + B	26–38	9	133 ± 12	2.03 ± 0.11
	N		17	60 ± 3	0.21 ± 0.02
Rabbit	C	15–21	7	455 ± 36	1.33 ± 0.10
	N		5	35 ± 2	0.17 ± 0.02
Chicken	C + B	10	4	685 ± 164	1.67 ± 0.21
	N		5	100 ± 3	0.41 ± 0.07

*C + B = diet supplemented with cholesterol plus bile salt
C = diet supplemented with cholesterol
N = normal controls

For purposes of comparison, some results obtained under similar conditions in rats, rabbits, and chickens are included in Table I. Since the responses of these species to cholesterol feeding are well known,[1] they are not dealt with in the text.

DISCUSSION

The average plasma cholesterol level of the hamsters fed cholesterol without bile salt was similar to that reported by Goldman,[2] but the hepatic accumulation of the sterol was found to be somewhat higher. Addition of bile salt to the diet further increased the cholesterol concentration in both plasma and liver.

*In a preliminary progress report, this focal hyperplasia was mentioned as "lesions"; at the time, only a first group of seven cholesterol-fed hamsters had been processed (Life Insurance Medical Research Fund, Annual Report for 1947).

The aorta of the experimental hamsters showed only negligible morphological changes, though the wall was deeply infiltrated with stainable fat. Goldman likewise found only insignificant structural changes in the aorta of hamsters fed cholesterol.[2] Altschul, on the other hand, observed large atheromas.[3]

These differences in the results obtained by the various authors are probably a consequence of differences in dietary conditions. In the experiments reported above, a solution of cholesterol in warm cottonseed oil was mixed thoroughly with the diet, and bile salt was added to the latter in order to increase absorption of the sterol from the gut. Goldman administered powdered cholesterol in gelatin capsules.[2] Altschul fed dried egg yolk powder with milk and "yolk cake."[3]

As a consequence of these dietary variations, the following factors were probably different in the experiments of the mentioned groups: (1) the amount of cholesterol absorbed from the gut and (2) the presence and nature of certain other components in the diet which might have had an effect of their own on the aorta. The latter point was recently studied by Altschul.[6]

When the response to cholesterol feeding of the hamsters is compared with those of the other species studied, it is evident that the accumulation of cholesterol in the liver did not follow the pattern of its blood level. In the hamsters the plasma cholesterol rose to only intermediate levels, but the hepatic sterol content reached extremely high values. In chickens, the plasma cholesterol was more than five times as high as that in rats, but the liver cholesterol levels were similar in these two species.

Regarding a relationship between the plasma cholesterol concentration and its effects on the aorta, it was found that macroscopic intimal cushions developed only in the chicken and the rabbit, the two species in which the plasma concentration rose to the highest levels. Among the other species, hamsters exhibited excessive fatty infiltration, while the rats, although showing the lowest of the experimental plasma sterol levels, developed, in a few instances, minor morphological changes.

SUMMARY

The effects of a diet containing 1 per cent cholesterol and 0.25 per cent bile salt were studied in hamsters. After feeding periods of sixteen to twenty-five weeks, the plasma cholesterol was significantly increased; in the liver an extremely high accumulation of the sterol and a severe fatty degeneration were observed. Sections of the aorta revealed an almost normal structure associated with considerable fatty infiltration. The effects observed in hamsters fed 1 per cent cholesterol without supplementation by bile salt were qualitatively similar, but somewhat smaller in extent. These results obtained with hamsters were compared with the effects of cholesterol feeding in three other species, i.e., the rat, rabbit, and chicken.

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USE OF ADRENOLYTIC DRUG, REGITINE, IN PHEOCHROMOCYTOMA

LLOYD T. ISERI, M.D.,* HUGH W. HENDERSON, M.D.,* AND JOHN WILLIAM DERR, M.D.**

DETROIT, MICH.

PHEOCHROMOCYTOMA is usually associated with characteristic paroxysmal symptoms and signs which are probably caused by epinephrine or epinephrine-like substances; however, it is now known that this tumor can also be manifested by sustained hypertension, the mechanism of which is obscure. It has been postulated that sustained hypertension is caused by the continuous release of nor-epinephrine,[1,2] but recent studies have shown poor correlation between the hypertension and the relative content of nor-epinephrine in the tumor.[3] It is possible that the abnormal tumor may secrete into circulation epinephrine or nor-epinephrine in proportions different from those obtained on assay of the tumor extract.[4] It has also been postulated that stimulation of the pituitary-adrenal cortical axis may be responsible for sustained hypertension.[5]

Whatever the mechanism of the abnormal physiology associated with pheochromocytoma, various adrenolytic drugs[4,6-10] have been used extensively in current studies of this tumor. Regitine, which produces blocking action on the receptors of excitatory sympathetic impulses, is the drug most recently studied. Grimson first reported the successful application of this drug during surgical removal of the tumor[10] and has extended its use to a total of four cases.[11] Recently, a patient with pheochromocytoma with sustained hypertension was treated and tested with intravenous, intramuscular, and oral Regitine† before and during operation. The use of oral adrenolytic drugs in the management of this disease has not been described before.

CASE REPORT

B. M., a Negro boy, 8 years old, was admitted to the hospital on Oct. 4, 1950, with impairment of vision. For about one year, the mother had noticed unusual episodes of sweating and precordial pulsations and loss of weight in spite of a ravenous appetite. About one month prior to admission, the patient began to have headaches, frequency of urination, recurrent abdominal pains and vomiting; when his school work failed, extremely poor vision was discovered. Mild periorbital edema was noticed two weeks prior to admission. There was no history of hematuria or dysuria. The family history was negative for hypertension.

From the Departments of Medicine* and Surgery** of Wayne University and City of Detroit Receiving Hospital, Detroit.

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†Regitine (Compound 7337) was furnished through the courtesy of Dr. F. F. Yonkman, Ciba Pharmaceutical Products, Inc., Summit, N. J.

Physical Examination.—The patient was alert, hyperactive, with a slightly underdeveloped skeletal structure. The blood pressure in the upper extremity was 210/170 mm. Hg and in the lower extremity, 260/200 mm. Hg. The eyelids were slightly puffy. The fundi showed grade 4 hypertensive retinopathy with hemorrhages, exudates, arteriolar spasm, and papilledema. Although the size of the heart was normal, the apical impulse was forceful, and soft systolic, apical, and pulmonic murmurs were heard. The lungs were normal. Deep in the left upper quadrant of the abdomen, near the midline, there was a small mass about 4 cm. in diameter. The liver, kidneys, and spleen could not be palpated. The extremities were negative. The patient weighed 26 kilograms, and the surface area of the body was found to be exactly 1.0 square meter.

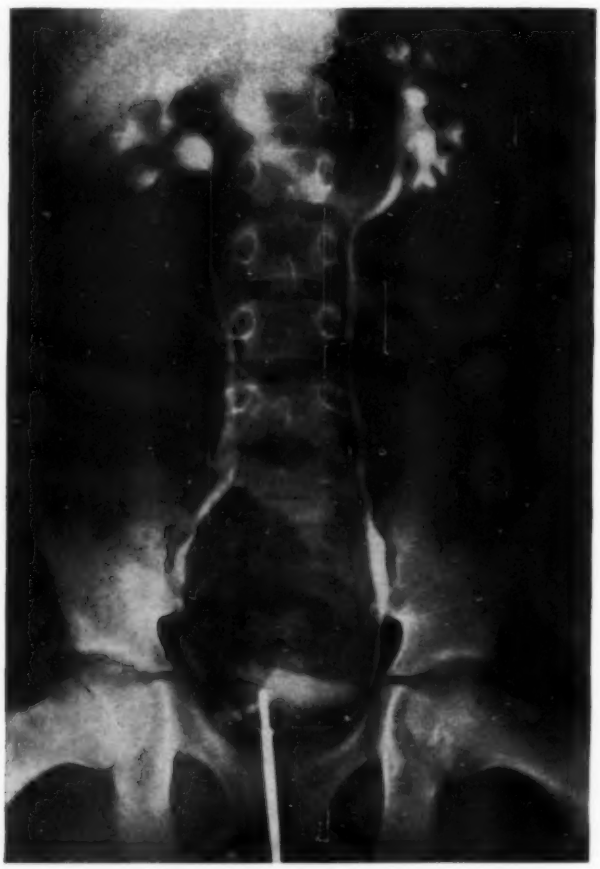

Fig. 1.

Laboratory Examinations.—The complete blood count was normal. The urine had a specific gravity of 1.002, contained no sugar, and showed a trace of albumin. Microscopic examination of the sediment was negative. The blood urea nitrogen was 19 mg. per cent. Fasting blood sugar was 80 mg. per cent. Basal metabolic rate was plus 31 per cent. Phenolsulfonphthalein excretion was 26 per cent in one hour. The standard and unipolar limb lead and precordial lead electrocardiograms showed evidence of left ventricular ischemia. The intravenous pyelogram demonstrated, on the right, a normal kidney and ureter and, on the left, outward rotation of the kidney and lateral displacement of the upper end of the ureter. These findings were also shown on a retrograde pyelogram and indicated the presence of a mass near the hilus of the left kidney (Fig. 1).

Clinical Studies and Observations.—The effects of various adrenolytic agents upon the hypertension and clinical condition of the patient were studied during an interval of twenty-nine days before operation.

Intravenous administration of 10 mg. of benzodioxane produced a sharp fall in pressure from 210/180 to 140/110 mm. Hg within two minutes, followed by a gradual rise to control levels in twenty-four minutes (Fig. 2, *A*). The systolic fall in terms of mean depth times duration was 672 mm. minutes and the diastolic fall 474 mm. minutes. This positive test confirmed the clinical diagnosis of pheochromocytoma.[6]

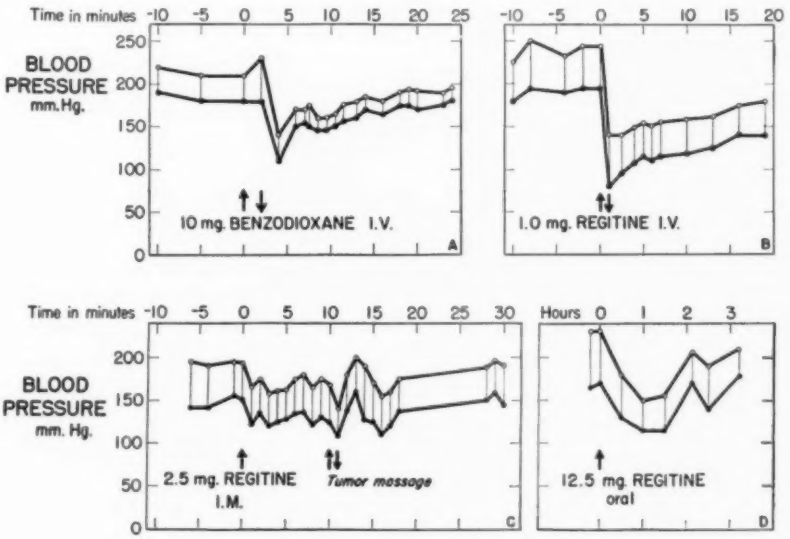

Fig. 2.

Attempts were next made to determine the effects of Regitine in different concentrations given by intramuscular, intravenous, and oral routes.

After withholding adrenolytic drugs for six hours, massage of the tumor mass for one minute caused a transient fall,* followed by a sharp rise in blood pressure (Fig. 3). This phenomenon

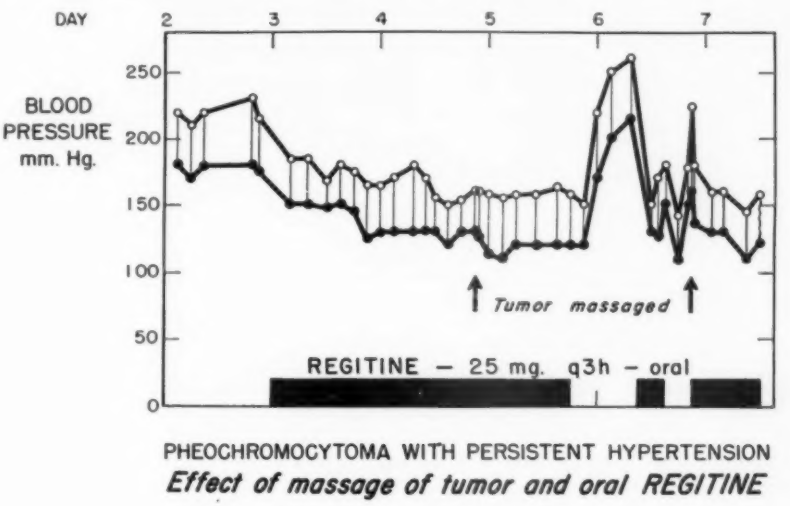

Fig. 3.

*Because of the transient nature, the fall in blood pressure is not illustrated.

was observed repeatedly during the preoperative period. Tumor massage for three minutes one-half hour after an oral dose of 25 mg. of Regitine produced no rise in pressure (Fig. 3), which would indicate a protective action by the drug; however, since blood pressures were not taken during the period of massage, demonstration of any initial fall in pressure was not possible.

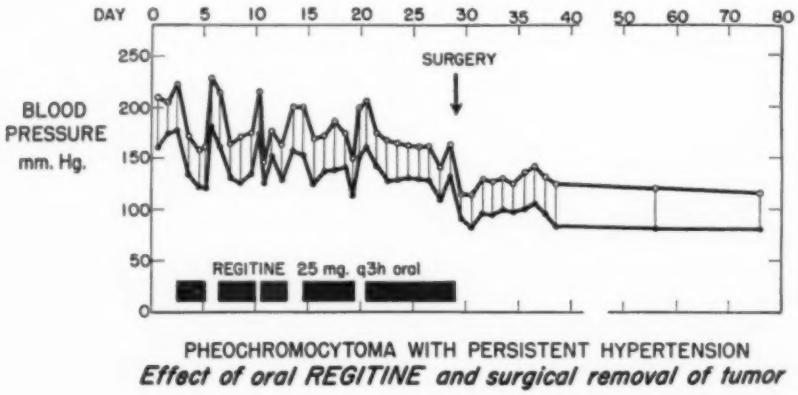

Fig. 4.

One mg. of Regitine was tested first by the intramuscular route. Before the injection could be given, the sight of the syringe and needle made the child cry. This psychic stimulation produced a transient fall in blood pressure from a control of 194/154 to 176/140 mm. Hg, followed immediately by a rise to 212/160, a reaction similar to the phenomenon observed during massage of the tumor mass. Soon after injection of 1.0 mg. of Regitine, the blood pressure fell to 162/128 mm. Hg and remained at this level for fifteen minutes.

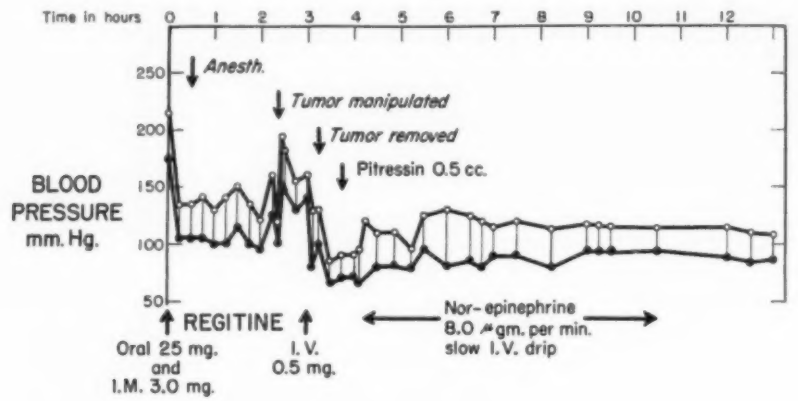

Fig. 5.

When 2.5 mg. of Regitine were given intramuscularly, the blood pressure fell from a control of 194/142 to 158/120 mm. Hg (Fig. 2, *C*). Systolic and diastolic pressures returned to control levels in about twenty minutes. However, the protective adrenolytic effect was not complete because exactly ten minutes after the injection of Regitine artificial stimulation of the tumor mass by massage immediately produced a transient fall in blood pressure to still lower levels, followed by a sharp rise in pressure to levels above the control base line values, as previously observed.

Intravenous injection of 1.0 mg. of Regitine resulted in an extremely sharp pressure fall from 240/190 to 140/80 mm. Hg which gradually returned to 180/140 mm. Hg within twenty minutes (Fig. 2, *B*). Ballistocardiographic tracings showed a 62 per cent increase in the I-J wave during the maximum fall in pressure, indicating that the stroke output had actually increased and that the fall in pressure was not due to a decrease in cardiac output. The cardiac rate, at the same time, increased from 140 to 170 beats per minute.

Oral administration of Regitine was tested next in 6.25 mg., 12.5 mg., and 25 mg. doses. With 12.5 mg. of oral Regitine, a satisfactory fall in blood pressure was obtained within one-half hour and persisted for about two hours (Fig. 2, *D*). Twenty-five mg. of Regitine produced a similar response, but the effect persisted for about three hours, while 6.25 mg. of Regitine produced only a transient and minimal fall in pressure.

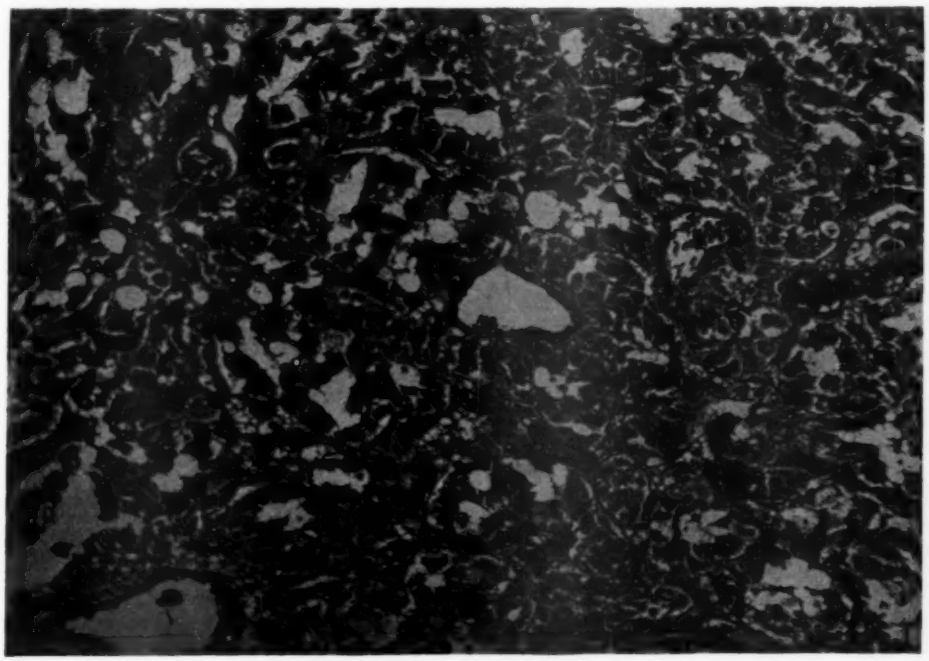

Fig. 6.

Regitine in a 25 mg. oral dose was given every three hours, day and night, to determine its effect in controlling the blood pressure and symptoms of the patient on a long-term basis. The blood pressure fell after the first dose and was maintained at approximately 165 mm. Hg systolic and 125 mm. Hg diastolic. Since this regimen was effective, the drug was continued for twenty-seven days during most of the preoperative period. When the drug was withheld for intervals to study its specificity, in each instance the blood pressure rose within six hours, and the extremities became cold and clammy within twelve hours after the last dose. Blood pressures were recorded before each dose, day and night, for the first twenty days and before each dose during the day only for the last seven days before operation; the mean pressures for each day during the entire hospital stay of thirty-nine days were determined and recorded (Fig. 4).

The patient improved markedly under oral Regitine management. Headaches and papilledema disappeared, vision improved considerably, and the soft exudates and hemorrhages partially resorbed. The arterioles were definitely less spastic than before. Abdominal pains and vomiting, which were present during the first two days after admission, never recurred. Electrocardiograms became normal.

Exploratory laparotomy, performed on the twenty-ninth day through a left upper, transverse abdominal incision, revealed a 3.7 by 3.5 cm., firm, encapsulated mass medial to the lower pole of

the left kidney, intimately adherent to the renal vein and displacing the ureter laterally and the renal artery anteriorly and superiorly. Both adrenals were in their usual location and were normal except for a slight decrease in size. No other abnormalities were noted.

Oral Regitine was continued until 3 A.M. on the day of operation. The doses due at 6 A.M. and 9 A.M. were inadvertently omitted, but that at 12 noon was given just before the patient was taken to the operating room. In addition, 1/12 gr. of morphine sulfate, 1/150 gr. of atropine sulfate, and 3.0 mg. of Regitine were given intramuscularly. The blood pressure, which had risen to 215 mm. Hg systolic and 175 mm. Hg diastolic because of the omission of Regitine, promptly fell to 135 mm. Hg systolic and 110 mm. Hg diastolic (Fig. 5). Without additional adrenolytic drug, the pressure then remained between 150/115 and 120/90 mm. Hg throughout the induction of anesthesia and during the initial surgical procedures. Two and one-fourth hours after adrenolytic drugs were given preoperatively, manipulation of the tumor produced a transient fall to 130/100 and then a rise to 200/150 mm. Hg, indicating that the adrenolytic effect was no longer complete. The blood pressure, however, decreased slowly to 155/130 mm. Hg over the following one-half hour period, during which manipulation of the tumor was inevitable due to its adherence to the renal vein. Decrease in systolic pressure was partially brought about by deeper levels of anesthesia, but the diastolic pressure remained relatively high.

Exactly three hours after the preoperative medications, 0.5 mg. of Regitine was given intravenously. The blood pressure fell to 130/80 mm. Hg and remained at this level for fifteen minutes until the tumor was completely isolated and removed; the blood pressure fell to 90/65 mm. Hg and remained at this level in spite of 0.5 ml. of Pitressin. A continuous drip of nor-epinephrine at the rate of 8 μg per minute was then started, and the blood pressure was maintained at approximately 120/95 mm. Hg for six hours. Following discontinuation of nor-epinephrine, the pressure remained stabilized at 120/80 mm. Hg. The immediate postoperative course was complicated by what appeared to be a perirenal hematoma, but this apparently resorbed without any difficulty.

Six weeks postoperatively, the patient had none of the symptoms which had occurred prior to hospitalization, and he had gained 6 pounds. His blood pressure was 115/80 mm. Hg, and massage of both renal areas produced no rise in blood pressure. The fundi had improved noticeably, as illustrated by serial color photography.

Pathological Report.—The specimen consisted of a tumor mass, weighing 39.3 Gm., well encapsulated except at that portion which was attached to the renal vein. The central portion showed necrosis and fibrosis, but the peripheral parts were well preserved and composed of firm pink tissue. Small areas of hemorrhage were present.

Microscopic examination (Fig. 6) revealed neoplastic epithelial cells arranged in nests, separated by fibrous tissue and interlaced by a rich capillary network. The individual cells, measuring uniformly about 20 microns in diameter, were poorly delineated. The cytoplasm was pink, granular, and in many areas hydropic. The nuclei were small, vesicular, and without visible nucleoli. Mitotic figures were rarely encountered. Two large, thick-walled veins contained neoplastic masses.

The chromaffin reaction with Zenker's fixative was negative, and the azocarmine staining reaction was weakly positive. The finding of neoplastic invasion of large-sized veins forced a tentative diagnosis of malignant pheochromocytoma.

*Experimental Studies of Tumor Extracts**.—In a dog weighing 13 kg., 2 c.c. of a fresh 1:10 saline extract of the tumor tissue produced a rise in blood pressure equivalent to that caused by 0.104 mg. of epinephrine (U. S. P.). Thus, the tumor contained pressor substances equivalent to 0.52 mg. per gram of tissue. After adrenergic blockade with S. Y. 28,† the same quantity of extract produced a depressor reaction, indicating primarily the presence of epinephrine. Since the tumor extract produced a somewhat lower depressor reaction than the test dose of epinephrine, the possibility is suggested that the extract contained slightly less epinephrine and more nor-epinephrine than is usually found in the U. S. P. epinephrine.

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*We are indebted to Dr. Victor A. Drill, Professor of Pharmacology, Wayne University College of Medicine, for the pharmacological studies and to Dr. Stanley Levey, Department of Physiological Chemistry, Wayne University College of Medicine, for the chemical determinations.

†Parke, Davis & Company, Detroit, Mich.

Chemical analysis of the extract, which had been stored in a frozen state, showed an epinephrine content of 0.15 mg. and a nor-epinephrine content of 0.524 mg. per gram of tissue. The ratio of nor-epinephrine to epinephrine was much higher than was expected from the assay studies. It is possible that conversion of epinephrine to nor-epinephrine occurred in the extract during the forty-day period of storage between its extirpation and chemical analysis.

DISCUSSION

It is probable that parenteral use of Regitine could prove to be valuable in the detection of pheochromocytoma, especially if the undesirable reactions which may accompany Benzodioxane[13,14] can be avoided. In the present case, the adrenolytic effect of 1.0 mg. of Regitine given intravenously was more pronounced than that of 10 mg. of benzodioxane and indicates a greater specificity of action. The response obtained by small, intramuscular doses of Regitine suggests that this route of administration also can probably be used for the detection of pheochromocytoma.

Because of its rapid and short action intravenously, Regitine has been used successfully both before and during operation by Grimson.[10,12] However, he used relatively larger doses and obtained a more prolonged action than observed in the present case where the development of transient tachycardia and profound pressure fall with a small intravenous dose made study with larger doses unwise. A combination of oral and intramuscular Regitine, timed to last only through the induction of anesthesia and course of operation, was successful with the addition of a small, single intravenous injection just prior to the removal of the tumor.

The use of oral Regitine, as described in this paper, for actual treatment of pheochromocytoma with sustained hypertension reduced the patient's blood pressure satisfactorily and led to specific clinical improvement within twenty-nine days. It is possible that oral dosage of the drug up to 50 mg. per square meter would have produced a more prolonged and a greater fall in blood pressure, since in this study raising the dose progressively from 6.25 mg. to 25.0 mg. per square meter increased the effect in linear proportion.

The success or failure of adrenolytic drugs in the testing or management of pheochromocytoma appears to depend on the nature of the circulating pressor substance. Apparently the pressor substance may differ from patient to patient and may conceivably be absent from the circulation.[3] Studies of the present case seem to indicate that epinephrine was the major substance initially liberated by the tumor into the circulation. The clinical manifestations of hyperhydrosis, tachycardia, and hypermetabolism in this patient correlate with epinephrine hypertension, as described by Goldenberg and co-workers.[3] During partial adrenergic block by Regitine, massage of the tumor mass and crying induced by fear produced an initial depressor response, indicating a discharge of epinephrine, immediately followed by a sharp pressor response, most probably related to a secondary discharge of nor-epinephrine. Thus, it is possible that the sustained hypertension in pheochromocytoma may be accompanied by discharge of epinephrine as well as nor-epinephrine and that the relative proportion of these two substances liberated into the circulation differs from time to time in each case.

Physiological studies made on the extract of the tumor indicated that epinephrine was present in appreciable amounts and correlated with the clinical studies

and symptoms. Chemical analysis, however, showed a preponderance of norepinephrine. The explanation for this discrepancy, apparently also noted by Beyer,[15] remains obscure.

Only a small quantity of pressor substances was found in the tumor tissue, agreeing with the meager staining reaction obtained on histological sections.

SUMMARY AND CONCLUSION

1. A case of pheochromocytoma with sustained hypertension is reported in which the patient was treated medically for twenty-nine days prior to surgery with an oral adrenolytic drug, Regitine, in doses of 25 mg. every three hours. The effects of oral and parenteral administration of Regitine in different doses were studied.

2. Preoperative administration of Regitine, 25 mg. orally and 3.0 mg. intramuscularly, controlled the blood pressure during the operation. A single intravenous dose of 0.5 mg. checked the transient rise during manipulation of the tumor. Postoperative fall in pressure was regulated adequately by slow norepinephrine infusions.

3. Studies indicate that epinephrine was the major pressor substance initially liberated by the tumor.

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SPLENOMEGALY ASSOCIATED WITH RHEUMATIC HEART DISEASE: ITS DIAGNOSTIC SIGNIFICANCE

W. L. BENNETT, M.D.,* DENVER, COLO., AND THOMAS M. DURANT, M.D.,** PHILADELPHIA, PA.

THE combined occurrence of a prolonged febrile state plus a palpably enlarged spleen in a patient with rheumatic heart disease is considered as being almost diagnostic of subacute bacterial endocarditis by most clinicians. The possibility that the fever could be on the basis of rheumatic activity and the splenomegaly the result of chronic passive congestion is generally considered quite unlikely, since it is usually assumed that congestion seldom leads to enlargement of the spleen of sufficient magnitude to result in its being palpable. While it is of great importance to emphasize any dictum which favors the early diagnosis of a disease such as subacute bacterial endocarditis, there is the possibility of carrying the dictum to the extreme of insisting upon the diagnosis even when no confirmatory evidence is obtained by means of blood cultures, thus leading to mismanagement of the case if the dictum is not based upon fact. The present study was carried out, therefore, to evaluate the diagnostic value of splenomegaly in patients with rheumatic heart disease.

From standard textbooks of cardiology the reader obtains considerable support for the concept of splenomegaly as an indicator of the presence of subacute bacterial endocarditis in cases of rheumatic heart disease. White,[1] in a discussion of the physical findings associated with heart disease, mentioned "splenomegaly, which is confirmatory of the diagnosis of subacute bacterial endocarditis." He did, however, describe a pulsating spleen as an occasional finding in aortic or tricuspid insufficiency. Levine[2] wrote that "a palpable spleen is rarely found...in valvular disease of the heart, even when there is congestive heart failure....When the abdominal viscera show evidence of passive congestion, splenic enlargement hardly ever reaches the point at which the organ becomes palpable on abdominal examination." In Stroud's *Diagnosis and Treatment of Cardiovascular Disease*[3] there is no reference to splenic enlargement in the presence of right heart failure, but emphasis is placed upon the value of splenomegaly in the diagnosis of subacute bacterial endocarditis, it being stated that it is "of particular importance when blood cultures are negative." Lewis'[4] opinion is somewhat at variance with the foregoing since he stated that "an enlarged spleen has long been regarded as a consequence of cardiac failure....A palpable spleen is not unusual in unaffected cases of mitral stenosis....In chronic heart disease,

From The Department of Medicine, Philadelphia General Hospital, Philadelphia.
Received for publication March 28, 1951.
*Formerly Resident in Medicine, Philadelphia General Hospital.
**Professor of Clinical Medicine, Temple University Medical School; Visiting Physician, Philadelphia General Hospital.

an enlarged spleen generally means infective endocarditis." Major's[5] view is that splenomegaly "occasionally occurs in combined mitral and tricuspid disease." Pathological experience (Moore,[6] Karsner,[7] and Anderson[8]) indicates that slight to moderate enlargement is associated with chronic passive congestion, the weights mentioned varying from 200 to 500 grams. Boyd[9] stated that "the enlargement (of the spleen) in mitral disease is inconsiderable in comparison with that of portal cirrhosis and can seldom be detected clinically."

In order to obtain more practical information concerning this important problem, we have studied the frequency of, and the possible reasons for, splenomegaly in eighty patients with rheumatic heart disease admitted to the Philadelphia General Hospital from October, 1948, to July, 1949. No selection of cases within this general category was exercised, and in so far as possible in a large city hospital with ten medical services, all patients suspected of having rheumatic heart disease were evaluated. The etiological diagnosis rested upon the usual criteria of history, physical findings, and the configuration of the heart as determined by orthodiagram or teleroentgenogram. When splenomegaly was found, the following studies were instituted: roentgen examination of the abdomen for spleen size, hemoglobin determination, total white blood cell and differential counts, and electrocardiographic study. Blood cultures were taken when indicated. Routine urinalyses, serological tests for syphilis, and blood sugar and urea nitrogen values were available. No exhaustive attempt to rule out all possible causes of splenomegaly could be made, but cirrhosis, infectious mononucleosis, leucemia, and malaria were kept especially in mind.

Definitely palpable enlargement of the spleen was found in eighteen of the eighty patients with rheumatic heart disease studied. In two of these, the splenomegaly could be attributed to a coexisting portal cirrhosis associated with long-standing alcoholism, and, in one of these two, the coexistence of rheumatic heart disease and portal cirrhosis was eventually confirmed by autopsy examination. In two other cases, subacute bacterial endocarditis was present and undoubtedly accounted for the splenic enlargement. In both of these instances therapeutic measures were ineffective, and the diagnoses were confirmed at autopsy. In still another case, a generalized lymphadenopathy was proved to be of tuberculous etiology by lymph node biopsy, and it is possible that the splenic enlargement was also due to tuberculous disease although this possibility was not definitely established.

There remain, then, following the exclusion of these five patients, thirteen in whom special search revealed no cause, other than congestion, for the splenomegaly. Subacute bacterial endocarditis was definitely ruled out, and there was no evidence of disease of the liver other than congestion or any abnormality of the lymphatic apparatus. The salient features of these thirteen cases are summarized in Table I. It will be noted that they do not differ materially from what would be expected of any average group of cases of advanced rheumatic heart disease. Four had definite clinical evidence of tricuspid valve lesions. Several had marked enlargement of the heart, but in three the cardiac size was within normal limits by orthodiagraphic examination. As would be expected, auricular

fibrillation was present in all but three patients, and these three had normal sinus rhythm. Case 6 was the only one in which auscultatory findings of mitral stenosis were not clearly evident.

TABLE I.

CASE	RACE	SEX	AGE	ADMISSION STATUS	CONGESTIVE FAILURE (DURATION)	HEART SIZE*			RHYTHM†	VALVE LESIONS‡
						TDC	TDH	% NORMAL		
1	W	F	60	Dyspnea; edema	2 years				A.F.	M-S, I
2	W	F	30	Ascites, cyanosis, dyspnea; no edema	2 years	245	163	25	A.F.	M-S, I A-S, I T-S, I
3	W	F	33	2 years intermittent fever	None	232	138	23	N.S.R.	M-S
4	W	F	54	Lobar pneumonia; cyanosis	2 years	240	146	15	A.F.	M-S
5	W	F	56	Ascites, dyspnea, cyanosis, slight edema	4 years	270	169	25	A.F.	M-S, I A-S, I T-I
6	W	F	19	Pregnancy, three months; dyspnea with exertion	3 months	248	133	7	N.S.R.	M-I? S
7	W	F	36	Joint pains, fatigue, weight loss, dyspnea on exertion	4 months	237	119	5	N.S.R.	M-S, I A-S
8	N	F	39	Dyspnea, edema	10 years	280	200	25	A.F.	M-S, I
9	W	M	20	Dyspnea, edema, cyanosis, cough, pain in left flank	At least 10 years	262	223	25	A.F.	M-S, I A-? S T-I
10	W	M	45	Dyspnea, cyanosis, pain in left flank	20 years				A.F.	M-S
11	W	M	69	Dyspnea, edema, ascites, cyanosis	9 years	275	187	25	A.F.	M-S, I T-I A-I
12	W	M	48	Dyspnea, cyanosis, chills, fever, cough, pneumonia	2 years	244	112	2	A.F.	M-S, I A-S
13	N	M	42	Gastrointestinal complaints (undiagnosed)	9 years	295	201	25	A.F.	M-S, I

*TDC = transverse diameter of chest in millimeters by orthodiagram
THD = transverse diameter of heart in millimeters by orthodiagram
% normal — from tables of Eyster
†A.F. = auricular fibrillation
N.S.R. = normal sinus rhythm

‡M = mitral
A = aortic
T = tricuspid
S = stenosis
I = insufficiency

Inasmuch as the main etiological factor in "cardiac" or congestive cirrhosis of the liver is prolonged and severe hepatic venous stasis[10] and since such cirrhosis might be considered an important factor in the development of splenomegaly in these patients, it is of great interest to note the duration of congestive failure in each. Ten of the thirteen had had symptoms of congestive failure for at least two years, and in five the duration had been greater than nine years. These patients, especially the latter five, may well be expected to have developed congestive cirrhosis. Autopsy examination was performed in Cases 9 and 11, and in each instance gross and microscopic examination revealed cirrhosis with interstitial and portal fibrosis in a degree compatible with long-standing "cardiac" cirrhosis. It is remarkable, however, that in one patient (Case 3) there were no symptoms or signs of congestive failure. This patient was admitted to the hospital because of long-standing (two years) intermittent fever believed to be of rheumatic origin. Four blood cultures revealed no blood stream infection. In

another patient (Case 6), there had been no symptoms of cardiac origin prior to pregnancy which was in the third month. In a third patient (Case 7), symptoms of congestive failure had been present for only four months before admission when cardiac insufficiency was apparently precipitated by reactivation of the rheumatic process. These last three patients, then, cannot be considered as having had long-standing, severe portal congestion. In the absence of autopsy findings, it cannot, of course, be definitely stated that these spleens were not enlarged on the basis of disease other than cardiovascular, but careful search revealed no clinical evidence of such disease.

Liver function studies were performed in five cases, and plasma protein determinations were available in a sixth. Mild to moderate impairment of liver function was observed in these cases, which has been reported previously as occurring quite frequently in severe rheumatic heart disease. In the entire group of eighty patients with rheumatic heart disease roentgen examination of the abdomen revealed three other instances of splenomegaly in which the spleen was not clinically palpable. In one other instance, the roentgenogram showed a normal-sized spleen, displaced downward, which had been palpable clinically. This case is not included in the group of thirteen patients with palpable spleens discussed above.

DISCUSSION

The facts which have been gathered in this study of eighty cases of rheumatic heart disease do not permit further speculation as to the etiology of splenic enlargement in such cases. Prolonged congestive phenomena are undoubtedly of importance in many, as indicated by the frequent presence of long-standing congestive failure, but such phenomena fail to explain all of the instances in which palpable splenic enlargement is present. Elucidation of other factors involved must await further understanding of splenic reactions to infection, toxins, and so forth.

The importance of this study relates to the surprising frequency of palpable splenic enlargement in rheumatic heart disease in the absence of subacute bacterial endocarditis and the importance that this fact must have to the clinician who has been in the habit of placing great stress upon the relationship of this finding to the diagnosis of endocardial infection. The frequency of palpable splenomegaly in this series is remarkably in keeping with the pathological studies of Fowler.[11] This investigator found that in forty-seven patients with rheumatic heart disease the average spleen weight was 210 grams with twenty weighing more than 200 grams and seven more than 300 grams. In fifty instances of hypertensive heart disease with failure, the average weight was 198 grams with nineteen weighing more than 200 grams and six more than 300 grams. Accepting the usual figure of 300 grams as the minimum for palpability, this suggests that splenomegaly might be anticipated clinically in 12 to 15 per cent of the patients with congestive failure. Such a figure is very comparable to the findings in the clinical series which form the basis of the present report.

SUMMARY

In a careful study of eighty patients with rheumatic heart disease, the spleen was found to be palpable in eighteen instances. In two the splenomegaly was due to subacute bacterial endocarditis, in two to coexisting portal cirrhosis, and in one it was probably the result of tuberculous dissemination. In the remaining thirteen cases (16 per cent), no cause, other than congestive failure, was found to explain the splenic enlargement, and clinical evidence of congestive failure was minimal or absent in a few of these cases.

While it is admittedly very important to consider subacute bacterial endocarditis in all cases of rheumatic heart disease with fever and splenomegaly, the clinician must not place too much reliance upon splenomegaly as a finding favoring such a diagnosis.

We wish to express our appreciation for the privilege of studying these patients to the other Chiefs of Medical Services at the Philadelphia General Hospital: T. G. Schnabel, R. S. Boles, D. N. Kremer, H. L. Goldburgh, W. G. Leaman, Jr., Frieda Baumann, C. M. Thompson, D. W. Kramer, and H. S. Flippin.

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A NEW METHOD IN ELECTROCARDIOGRAPHIC TECHNIQUE FOR USE IN PATIENTS WITH SOMATIC TREMOR

NATHAN GLAUBACH, M.D.

SANTA MONICA, CALIF.

THE problem of electrocardiography in patients with marked somatic tremor has received little attention. Artifacts due to muscle tremor receive mention in the various texts on electrocardiography, but chiefly from the standpoint of recognition. Elimination of this artifact by inducing sleep has been mentioned,[1] but a review of the literature fails to reveal any specific method for control of muscle tremor for electrocardiographic purposes or electrocardiographic methods which would obviate the effect of muscle tremor on the electrocardiogram.

The effect of somatic tremor on the electrocardiogram is to render it of little or no value. The rhythm, conductive mechanism, and configuration of the electrocardiographic pattern are obscured or lost as a result of the vibratory motion or violent oscillations of the string or stylus. Misinterpretation and lack of interpretation are not infrequent. Confusion with auricular flutters is also not uncommon. The need exists, therefore, in patients having marked somatic tremor, for a method of recording readable electrocardiograms.

Electrocardiography during sleep has been offered as a solution to this problem,[1] and many investigations have been done with electrocardiography during anesthesia. However, these studies were carried out to determine the effect of various anesthetic agents on the heart as recorded on the electrocardiogram. The resultant findings have been somewhat conflicting. Galambos[2] has used the electrocardiogram as a means of studying tremors and the effects of bulbocapnine in postencephalitic Parkinsonism. Betlach,[3] using Pentothal Sodium in doses in excess of that required for anesthesia, came to the conclusion that this agent was safe and had very little or no significant effect on the heart as recorded on the electrocardiogram. Volpitto and Marangoni,[4] using the same agent, found that where no cardiac irregularities existed, none were produced, and where cardiac irregularities did exist, they were not altered by the use of the drug. Kohn and Lederer[5] concluded that Pentothal Sodium had little or no significant effect on the heart as shown on the electrocardiogram. On the other hand, Widenhorn, Volini, and McLaughlin[6] arrived at an opposite conclusion, reporting increased heart rate, P-R interval shortening, extrasystoles in a bigeminy rhythm, and T-wave inversion in Leads I, II, and III in two-thirds of their animals.

From the Medical Service, Wadsworth General Medical and Surgical Hospital, Veterans Administration Center, Los Angeles.

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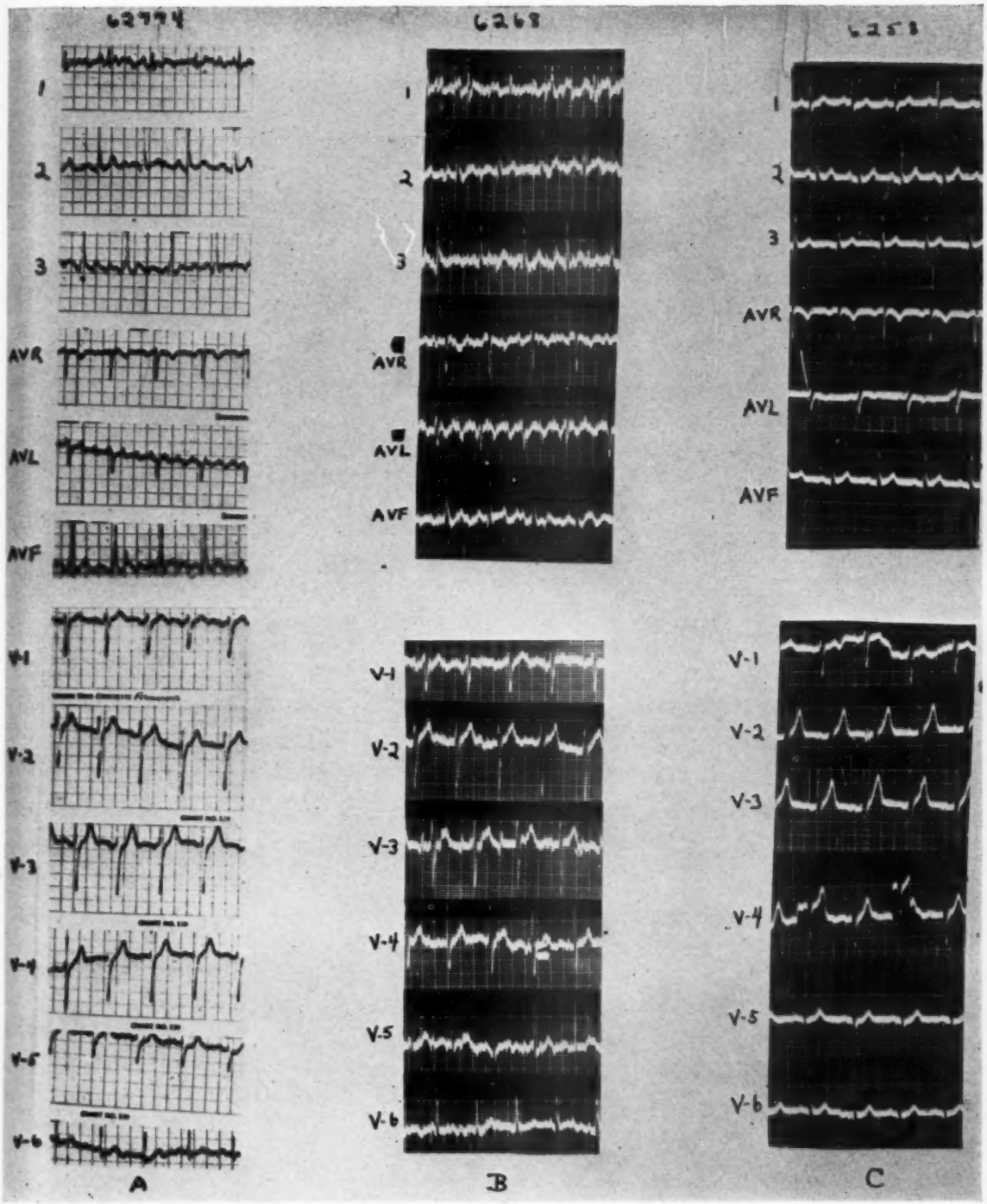

Fig. 1.—This patient, with a typical Parkinsonian tremor of the upper extremities, had previously had an electrocardiogram (No. 62774, *A*) which had been interpreted as an impure auricular flutter with variable block. A sleep tracing under influence of Sodium Amytal (No. 6258, *C*) revealed a normal pattern. No. 6268, *B*, was run as a control at the time of the sleep record.

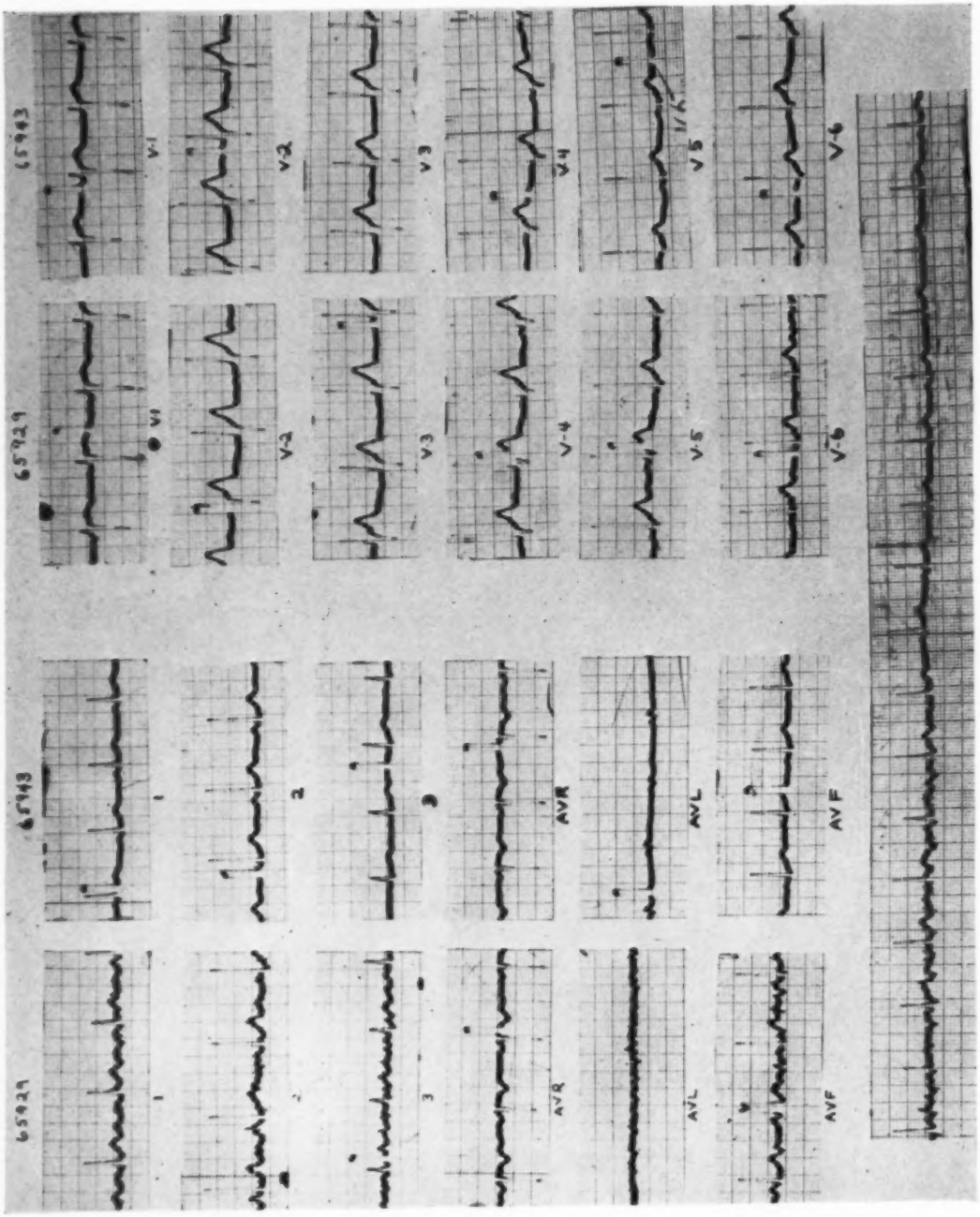

Fig. 2.—A sleep record (No. 65943) done under the influence of Pentothal Sodium on this patient afflicted with Parkinson's disease reveals a normal pattern. Prior electrocardiograms, of which No. 65929 was one, had been interpreted as probably normal, but Leads I and III suggest auricular flutter. The long strip at the bottom shows the transition to the artifact-free tracing.

Gruber, Haury, and Gruber[7] arrived at similar conclusions, finding that the use of thiobarbiturates produced cardiac arrhythmias in every animal. However, as pointed out by Betlach,[3] the cardiac irregularity disappeared if the anoxia

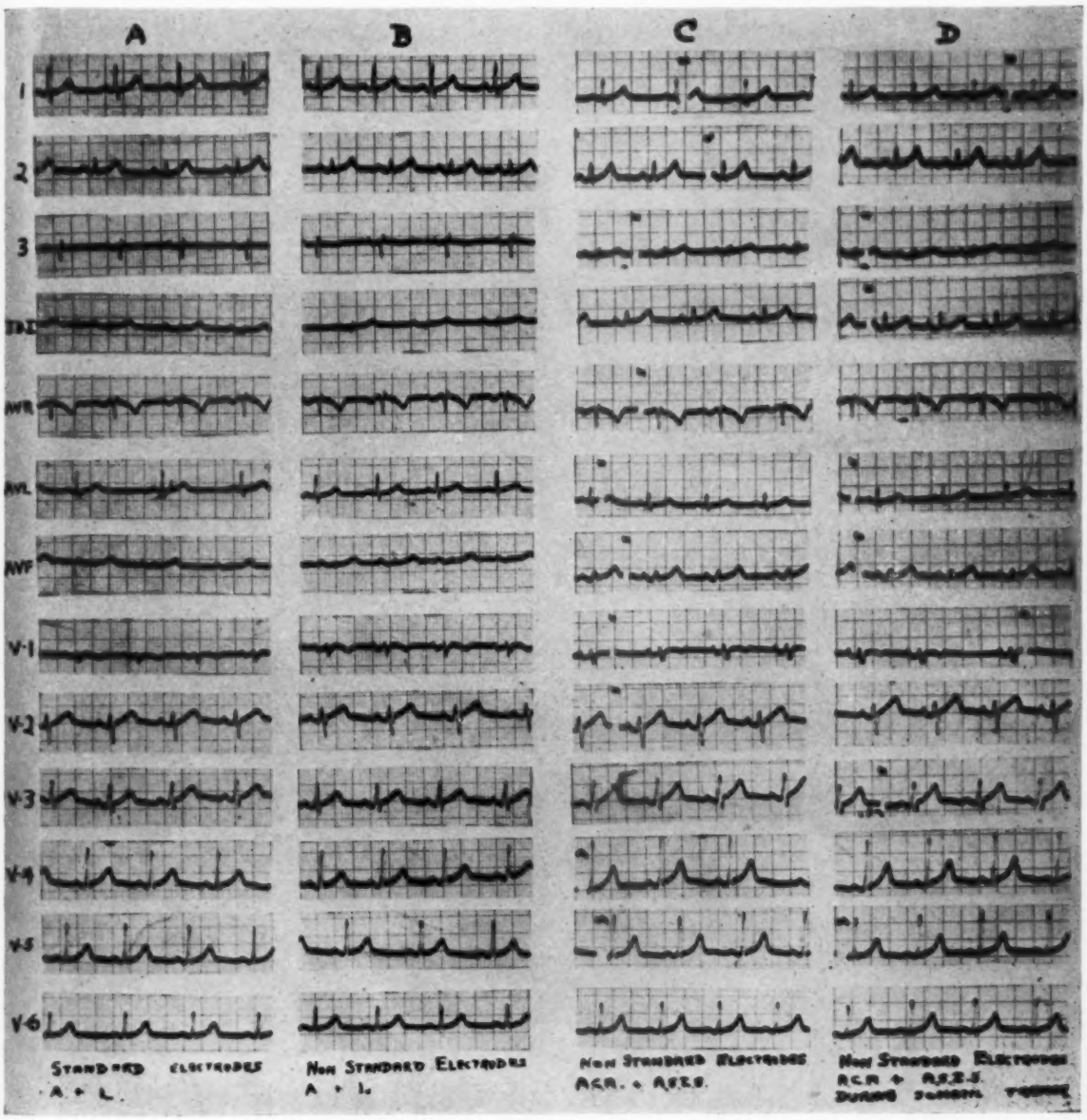

Fig. 3.—*A* represents an electrocardiogram done in the usual manner, using standard electrodes attached to the extremities. *B* represents an electrocardiogram made with the electrodes illustrated in Fig. 4 and attached to the extremities. This is to prove that the change to this type of electrode did not influence the electrocardiographic pattern. *C* is a recording with the new electrodes attached over the supraglenoid tubercles and anterior superior iliac spines. *D* is a recording made with the subject moving the extremities in a manner similar to a Parkinsonian tremor to note the effect of the tracing. This was experimental proof that the method was worth further investigation. Subsequently, clinical studies were made.

concomitant with the use of the drug was alleviated by the inhalation of oxygen. Bower, Burns, and Mengle,[8] using Sodium Amytal as an anesthetic agent, concluded that it had no significant effect on the diseased myocardium as shown by electrocardiography.

From the foregoing, it would appear that with proper precautions, Sodium Amytal and Pentothal Sodium were safe agents, having little effect on the heart, and could be used as sleep-inducing agents for purposes of electrocardiography.

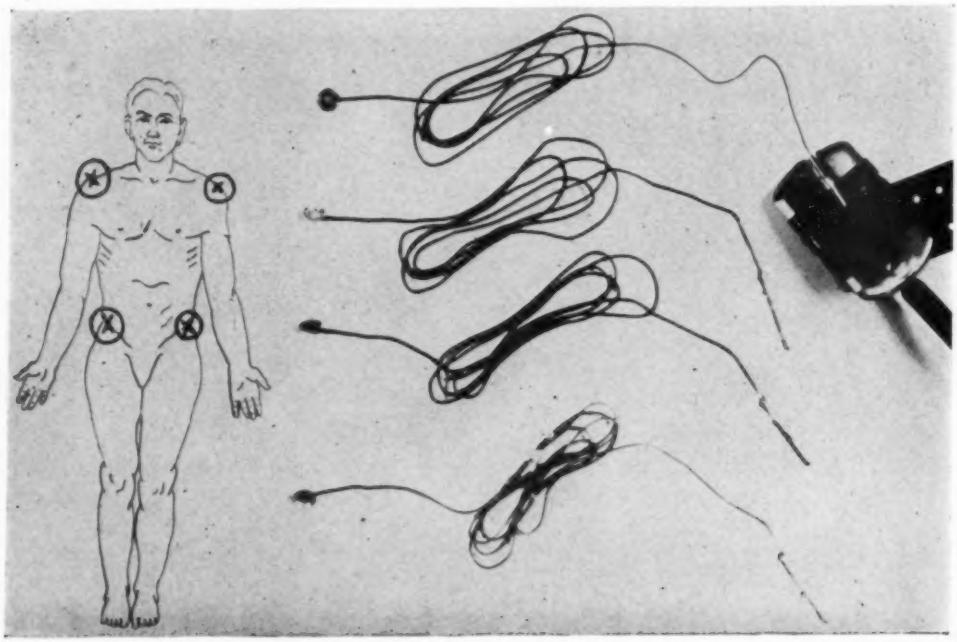

Fig. 4.—The electrodes illustrated are the same as those used for electroencephalography. After the usual skin preparation, they are applied over the supraglenoid tubercles and anterior superior iliac spines. The metal tips are inserted through one of the perforations of the rubber strap which has been wound around the standard electrode of the appropriate limb lead. Care must be used to avoid accidental grounding or touching other parts of the body. Electrocardiography is then carried out as usual.

These drugs have been used successfully with results as illustrated in Figs. 1 and 2. However, for reasons given below, this method is not considered with favor. There are numerous precautions and contraindications to be considered. These are ably presented by Adriani[9] and are as applicable to their use as sleep-inducing agents for purposes of electrocardiography as to their use for anesthesia. Patients must be selected with care, thus eliminating those in whom contraindications exist. At the time of electrocardiography, the presence of at least two people is required, viz., the physician and a technician. It is time consuming, a major consideration in large institutions where a great deal of work with limited personnel is a factor. A method was therefore sought which would be practical, could be carried out easily by one person, would eliminate the use of drugs, and give reliable results.

In examining patients with Parkinson's disease, it was noted that there was a minimal amount of tissue movement over the supraglenoid tubercles and over the anterior superior iliac spines, even though there was marked muscle tremor and

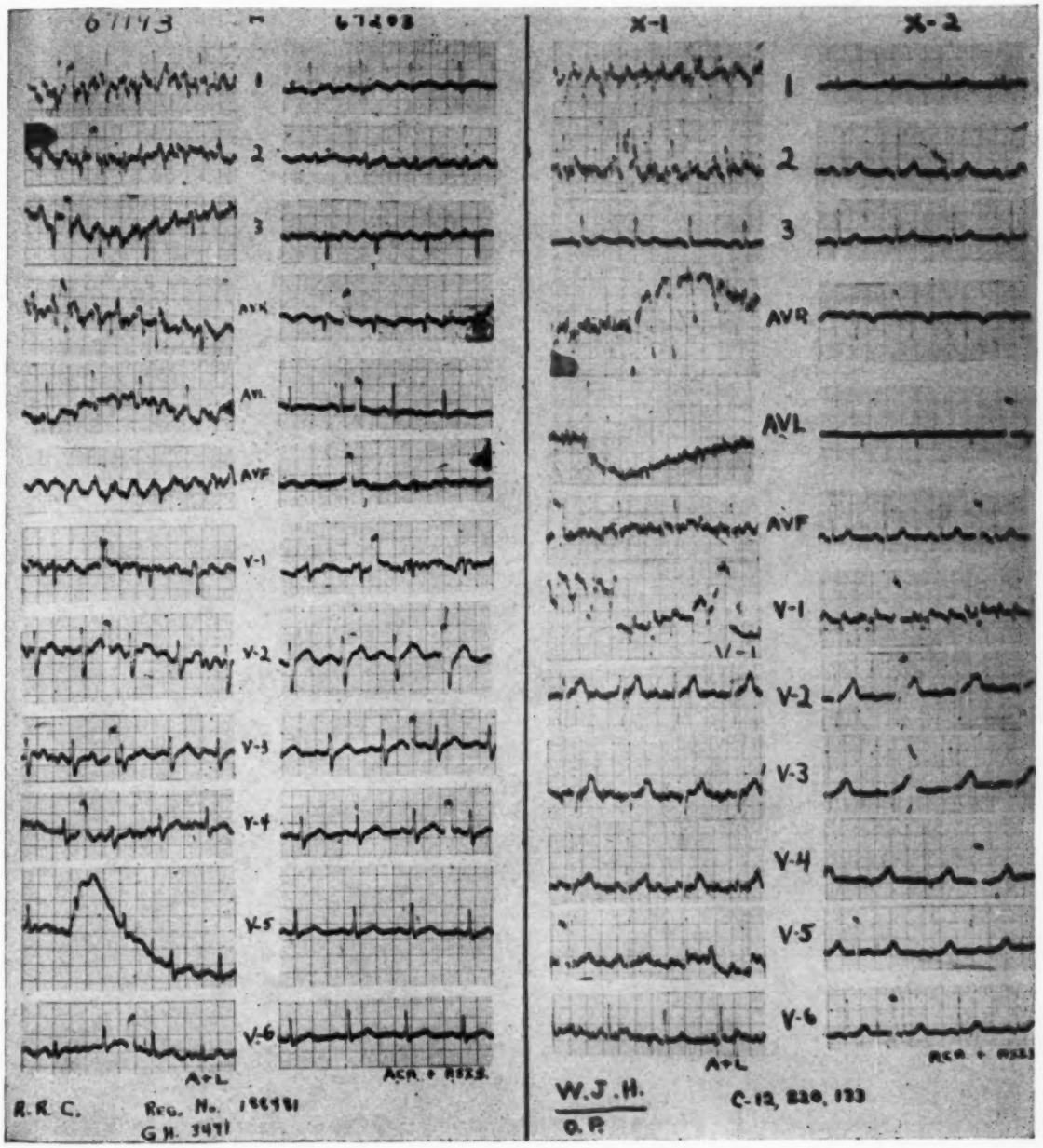

Fig. 5.—No. 67193 and No. X-1 were recorded on patients R. R. C. and W. J. H., respectively. Although both had marked Parkinsonian tremors, the left arm of W. J. H. was not involved. No. 67203 and No. X-2 revealed a remarkable improvement in the appearance of the tracings as obtained by the method described in this article.

movement of the extremities. From the standpoint of electrocardiography, this was a fortunate observation in that it suggested sites for electrode application where the tremor would have a minimal effect. In addition, it would result in electrocardiographic patterns similar to those obtained with electrodes fastened

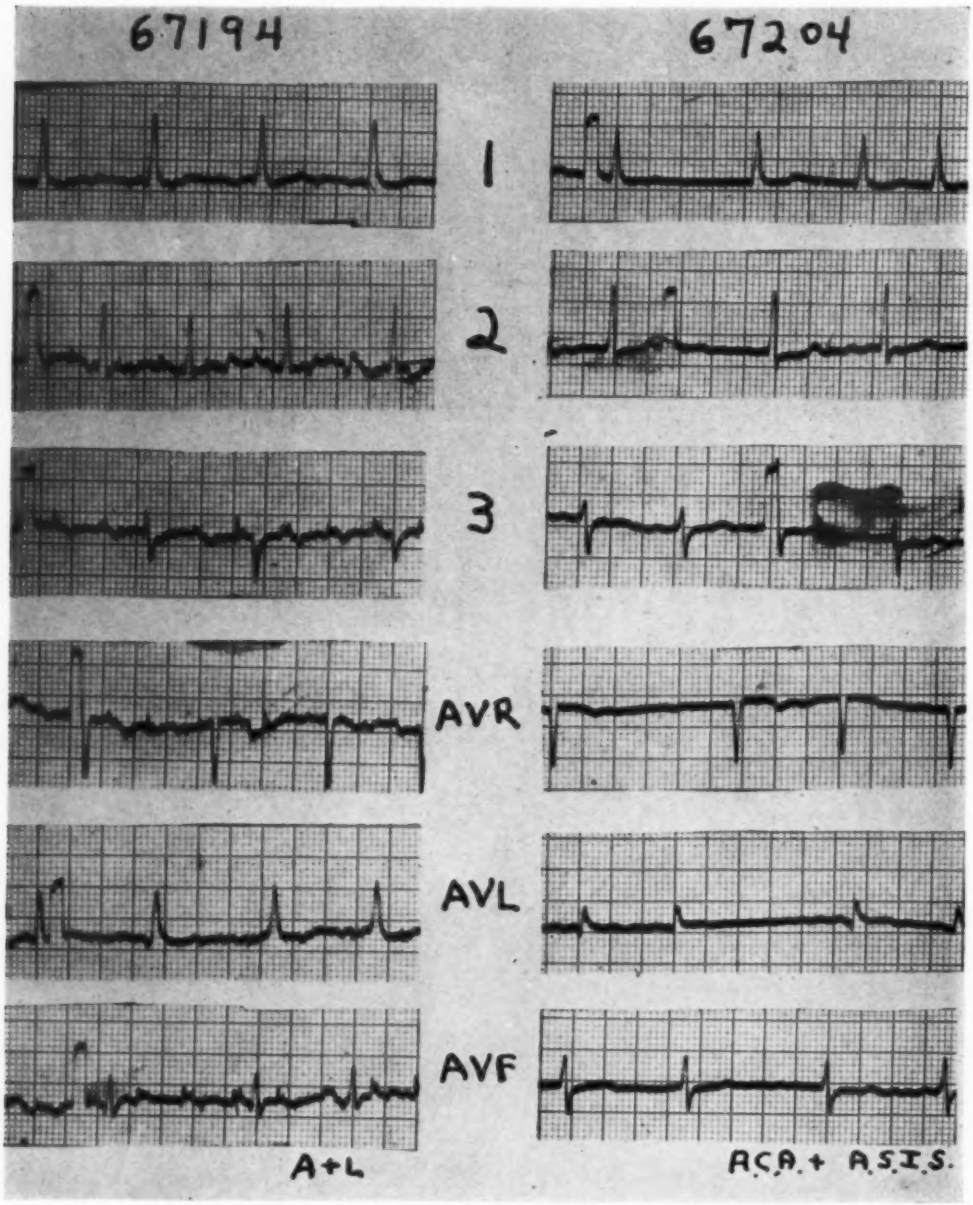

Fig. 6.—No. 67204, obtained by the method described in this article, is technically a much better tracing and reveals the pattern of auricular fibrillation much more clearly than that shown in No. 67194, taken at the same time, but with the usual technique.

to the extremities and would permit the continued use of the presently accepted terminology (Fig. 3). Since the standard electrodes would not permit ease of application in these areas, those used for electroencephalography were adapted for use. After the usual skin preparation, the electrodes were attached with short strips of adhesive tape, scotch tape, or with collodion. By attaching the wire from each of these electrodes to the appropriate limb lead, electrocardiography could be done as usual (Fig. 4).

This method has resulted in improved electrocardiograms in all cases in which it has been utilized (Figs. 5 and 6). In some instances of neurological disease where body movement is exaggerated and uncontrollable, this method is inoperable. In such cases, a sleep tracing should be done, provided no contra-indications to the use of the sleep-inducing agent exist.

SUMMARY AND CONCLUSIONS

1. A method of electrocardiographic technique is offered which reduces the effect of muscle tremor and results in readable tracings.

2. Its patterns are practically similar to those obtained with electrodes attached to the extremities and thus permit retention of terminology now in use.

3. It is useful in the majority of patients in whom muscle tremor is present and the need for electrocardiography exists.

4. It is practical, can be easily carried out by one person, eliminates the need for hypnotic drugs, and gives reliable results.

5. The use of sleep-inducing agents for purposes of electrocardiography is not recommended as a routine procedure and should be used in selected cases only.

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Review of Recent Advances

DIETOTHERAPY IN HYPERTENSIVE DISEASE

SEYMOUR H. RINZLER, M.D., F.A.C.P.

NEW YORK, N. Y.

DIET therapy for arterial hypertension has been advocated practically as long as knowledge of this illness has existed. The use of restricted salt intake was promulgated in 1904 by Ambard and Beaujard[1] and in 1922 by Allen and Sherrill.[2] The ideas of Allen were vigorously contested and lay dormant until about 20 years later when diets[3-6] in which the sodium intake was restricted to 200 mg. or less per day began to enjoy a wide clinical and experimental usage.

A real boost in dietary treatment of hypertension was given by Kempner,[7] who, in 1940, began to treat patients with hypertensive vascular disease with a diet containing 2,000 calories, 15 to 20 Gm. of protein, 4 to 6 Gm. of fat, no cholesterol, and 150 mg. of sodium, the main constituents being rice and fruit. Fluids were limited to 700 to 1,000 c.c. a day. Supplementary vitamins included vitamin A, 5,000 units, vitamin D, 1,000 units, thiamin chloride, 5 mg., riboflavin, 5 mg., niacinamide, 25 mg., and calcium pantothenate, 2 mg.

CALORIC RESTRICTION

It was noted that one of the results of Kempner's regimen[7] was the attendant reduction in weight on a reduced caloric intake. It was not unusual for the weight to decrease more or less markedly during the first 20 days. This raised the question of whether or not weight reduction was a factor in lowering blood pressure. Reports have been made[8,9] on blood pressure reduction in arterial hypertension after controlled loss of weight. In Adlersberg's series,[8] 20 of 35 patients (57 per cent) had reductions of blood pressure from levels over 155/100 mm. Hg to those below this level after weight loss. Thirty-four normal men subjected to experimental starvation for 6 months on a diet consisting of slightly less than 1,600 calories daily showed a decrease in the mean systolic blood pressure of 11.1 per cent and of the mean diastolic blood pressure of 7.73 per cent.[10]

The last war presented a massive unplanned clinical background to test the effect of caloric reduction on the level of blood pressure. From September, 1941, to March, 1942, the city of Leningrad was under siege, and a state of semi-starvation ensued. The Russian report has been analyzed by Brozek, Chapman, and Keys.[10] During this period there was not only a reduction in the type of patients hospitalized for hypertension, but there were also "significant changes

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in the clinical picture of hypertension and its manifestations. In a large number of patients who exhibited long-standing chronic hypertension, the blood pressure was reduced to a normal or near normal level. Furthermore, symptoms commonly associated with hypertension such as headache, dizziness, and dyspnea on exertion decreased in intensity or completely disappeared."

Reports from other parts of Europe[11,12] and studies from concentration camps[13] where the same problem existed confirmed the findings in Leningrad. In the 2 years following the famine in Leningrad, an increase in the incidence of hypertension was again noted. This was attributed to the "hypertensive" effect of food given during a period of recovery from semistarvation rather than to an increase in sodium intake, because there never was a reduction in the sodium intake comparable to the presently used sodium diets. Using 140/90 mm. Hg as the normal blood pressure, a comparison of the blood pressures of 10,000 persons, prewar (1940) and after the siege (April, 1943), showed that there was a rise in the percentage of elevated blood pressure in all age groups. In the age groups of 20 to 29 years and 30 to 39 years the increase was approximately fourfold. This rise in the incidence of hypertension could not be entirely attributed to the changes of age and sex distribution of the wartime population of the city.

These data demonstrate the possibility of lowering blood pressure by caloric restriction even under conditions of great nervous strain such as war presents.

RICE DIET AND LOW-SODIUM DIET

In 1940, Kempner began using the rice diet in the treatment of hypertensive vascular disease. By 1948, he had treated 500 patients who had been on the diet 4 to 300 days. These patients included those with and without disturbances of renal function. There was no statement made as to the nature and duration of the control periods nor as to the duration of the hospital period. Sixty-two per cent of the 500 patients showed a decline of 20 mm. Hg or more in the mean blood pressure. One hundred and twenty-five of these patients had a reduction in blood pressure to 145/95 mm. Hg and below. Great medical interest was evinced by this report because diminution in heart size, changes in the electrocardiogram toward normal, and disappearance of hemorrhages, exudates, or papilledema in the eyegrounds were reported.[7]

Certain questions were asked. (1) Was the improvement due to the total nature of the rice diet, or was it due to individual factors making up the diet, such as the low sodium, low protein, and low calories, or to some unknown factor in the rice itself? Mention has already been made of the role of caloric restriction. To date no adequate factor has been found in the rice itself to explain any hypotensive action. (2) Can an objection be raised to data collected without adequate control periods or to data not obtained under hospitalized conditions? This point is raised because it is a known fact that the blood pressure will fall spontaneously during control periods on bed rest. (3) May not the return of blood pressure to normal in some of these cases be attributed to spontaneous remissions during the natural course of hypertensive vascular disease?[14] (4) Are there any deleterious effects of the rice or low-sodium diets?

TABLE I. EFFECT OF RICE AND LOW-SODIUM DIETS ON BLOOD PRESSURE IN HYPERTENSIVE VASCULAR DISEASE

AUTHOR	NO. PATIENTS	AMBULATORY OR HOSPITAL	CONTROL PERIOD (DAYS)	DAYS ON DIET	TYPE OF DIET	BLOOD PRESSURE REGARDED BY AUTHOR AS GIVING SATISFACTORY RESPONSE	NO. PATIENTS WITH BLOOD PRESSURE REDUCED TO 155/100 MM. Hg OR LOWER
Viersma[17]	14	Hosp.	8-120; average, 28 in 12 patients	1 patient, 2½ years; 1 patient, 1 year; others 43-159 days	400 mg. of sodium daily	Not given	2
Bryant and Blecha[20]	100	Amb.	?	3 years	200 mg. of sodium daily	155/95	20
Flipse and Flipse[18]	32	Amb.	None	7–42	Rice	Not given	5
Contratto and Rogers[22]	34	Amb.	3 years	90–180	Rice	150/100	16
Rosenberg, Rosenthal, and Rosenbluth[21]	9	Hosp.	30	30–60	Rice and low salt	139/95	1
Canter[19]	30	Amb.	None	210–365	Rice	Not Given	18
Kempner[7]	500	Amb.	?	4–300	Rice	145/95	125
Schroeder[24]	22	Hosp.	14–180	15–50	0.5 to 1.0 Gm. of sodium chloride	150/100	5
Loofbourow[23]	56	Amb.	60	21–300	Rice	150/100	4
Chasis[25]	12	Hosp.	14–79	14–98	Rice	146/86	1 (?)
Watkin[26]	50	Hosp.	28–140	35–133	Rice	Not given	14*
Corcoran[27]	15	Hosp.	14–98	14–112 (1 patient, 538)	Rice or 200 mg. of sodium	Not given	2

*This is based on 47 patients, since 3 had blood pressures of 155/100 mm. Hg or below at the end of the control period.

The answers to these questions were sought in the experimental and clinical studies that followed Kempner's reports. The data which have accumulated since 1945 will be presented below, and the clinical conclusions are partially summarized in Table I.

In 1945, Grollman and Harrison[15] published a study on rats with experimental hypertension in which they attempted to identify the pressor ion. They found that a low-salt diet caused a marked decrease in the blood pressure of the animals and that the addition of as little as 0.5 Gm. per cent of salt partially prevented the hypotensive effect of the diet. The addition of 2 Gm. per cent of salt completely abolished the effect. When sodium chloride was replaced with potassium chloride, the blood pressure decreased as promptly as when the ordinary low-salt diet was used. They concluded, therefore, that the pressor effect was caused by the sodium ion. Dick and Schwartz,[16] in 1947, maintained 12 hypertensive dogs for 2 weeks on the Kempner regimen. These dogs had been hypertensive for 2 to 4 years before the rice diet was instituted, and a significant reduction of arterial pressure was found in the animals with the highest initial levels.

From an experimental point of view, therefore, a fall in blood pressure in hypertensive animals could be induced by either a rice or low-salt diet. Since 1945, successive reports of the use of these diets in man have been published. Viersma[17] studied the effects of a daily diet containing 400 mg. of sodium on the blood pressure of 14 patients who were hypertensive. Eight of these patients had essential hypertension, 2 had chronic nephritis, and 4 had malignant hypertension. In 7 of the 10 patients without malignant hypertension the blood pressure became lower, the systolic declining 40 mm. Hg or less and the diastolic 26 mm. Hg. There was no change in the blood pressure in those with malignant hypertension. Observations on 1 patient in the essential hypertension group were made for 2½ years, on another for more than 1 year, and on the remainder for an average of 72 days.

Flipse and Flipse[18] evaluated the effects of the rice diet on 32 ambulatory patients who were able to follow the diet strictly. No control period was noted, and observations on the diet lasted from 7 to 42 days. Of these 32 patients, 5 had a fall in the blood pressure to 155/100 mm. Hg or below from previously higher levels.

Canter[19] treated 30 patients with an average blood pressure of 206/111 mm. Hg with the rice diet for 7 months to 1 year. There was no control period, and these patients were ambulatory. Of the 30 patients, blood pressures of over 155/100 mm. Hg were present in 25 before treatment. Of these 25, 18 had a drop in blood pressure to 155/100 mm. Hg or less after treatment.

In 1947, Bryant and Blecha,[20] using a diet supplying 2,200 calories, 70 Gm. of protein, 3 L. of fluid, and 0.2 Gm. of sodium per day, treated 100 patients with hypertension on an ambulatory basis. There was no control period noted, but no pretreatment blood pressure was below 170/100 mm. Hg. The treatment lasted for several weeks to 1 year. There was a drop in blood pressure to 155/95 mm. Hg in 20 per cent of the 100 patients, and in an additional 15 per cent, the diastolic pressure fell to 95 mm. Hg. The use of a 70 Gm. protein diet is

to be contrasted with the 20 Gm. protein diet of Kempner. The reduction of the blood pressure to 155/95 mm. Hg or lower in 20 per cent of the patients on the former diet compares well with the decrease of blood pressure to 145/95 mm. Hg in 25 per cent of the patients on the low-protein Kempner regimen.

Rosenberg, Rosenthal, and Rosenbluth[21] studied 9 patients with essential hypertension who were hospitalized throughout the period of study and who were followed during control periods averaging 1 month. Of 7 patients on a low-sodium diet (300 mg.), no statistically significant fall in the blood pressure was reported in 3. In the remaining 4, diastolic pressure reductions of −11, −9, −19, and −12 mm. Hg, respectively, were regarded as significant. Of 5 patients on the rice diet, 3 had significant falls in blood pressure, the diastolic pressures in these patients falling −11, −10, and −10 mm. Hg, respectively. Only 1 patient had a blood pressure drop to normal. This patient had a pretreatment level of 166/104 mm. Hg which fell to 139/95 mm. Hg on the low-salt diet and 132/86 mm. Hg on the rice diet. The duration of the treatment averaged 30 to 60 days.

Contratto and Rogers[22] studied 34 patients with known hypertension for at least 3 or more years. These patients were treated with the rice diet for between 90 to 180 days on an ambulatory basis. The blood pressure during the control period averaged 210/120 mm. Hg and after 3 months on the rice diet averaged 158/100 mm. Hg. The same average figure was obtained at the end of the 6 month period. A fall in the systolic blood pressure to 150 mm. Hg or below and in the diastolic to 100 mm. Hg or below was recorded in 16 patients. A drop of 20 mm. Hg in the diastolic pressure was found in 8 patients.

Loofbourow and co-workers,[23] after a control period of 60 days, maintained 56 ambulatory patients on the rice diet for 21 to 300 days. Sixteen patients adhered strictly to the diet, and of these 4 patients had a fall in blood pressure to 150/100 mm. Hg or lower. Six of the 16 patients (37 per cent) showed a drop in the diastolic pressure of 20 mm. Hg or more.

Schroeder,[24] in St. Louis, studied 22 hypertensive patients on either the rice or the low-sodium diet. The control periods lasted 14 to 180 days in the hospital, and treatment lasted from 15 to 50 days with an average of 31 days. There was improvement in 9 patients. Three of these 9 patients had a diet consisting of 0.5 Gm. of salt and 6 of these patients 1.0 Gm. of salt. Five of these 9 patients had falls in the blood pressure to 150/100 mm. Hg or below. The diastolic pressure fell 20 mm. Hg or more in 4 patients. The 6 patients with the best response to salt restriction were all women and all obese. This obesity appeared rapidly at puberty and after childbirth and was confined to the trunk, face, and proximal parts of the extremities. They had difficulty in attempting to lose weight, and hirsutism and menstrual irregularity were found in some. The general body configuration of these patients resembled in some aspects that seen in Cushing's syndrome, and Schroeder concluded that the low-salt diet might be of value to these "pseudo-Cushing's syndrome" patients.

Chasis[25] and associates studied 12 patients who were in the hospital during a control period of 14 to 79 days and on the rice diet for 14 to 98 days. In 4 of the 12 subjects the average systolic and diastolic pressure decreased relative

to the control pressure. One patient had a fall of the blood pressure to normal, but this occurred 24 hours after the rice diet was begun, and it was questioned as to whether this fall could be attributed to the effect of the rice diet. The authors concluded that in none of these 4 patients could the decrease in pressure be attributed to the rice diet. They stated that in the estimate of any form of therapy "reduction in blood pressure can be considered as significant only when the systolic and diastolic pressures fall from pre-existent and well established hypertensive levels into and remain in the normal range."

Watkin and associates[26] studied 50 patients who were in the hospital during a controlled period of 28 to 140 days and on the rice diet for from 35 to 133 days. In 17 of the 50 patients (34 per cent), the blood pressure was 155/100 mm. Hg or below at the end of the study. But of these, 3 already had pressures at this level at the end of the controlled period. Actually then, 14 of 47 patients (29 per cent) had a fall of blood pressure to 155/100 mm. Hg or below from a previously higher level.

These reports represent some of the larger series of investigations on the rice diet and low-sodium diet in hypertensive vascular disease. Interpretation of these reports must be based on criteria used in estimating the significance of blood pressure response. As far as absolute fall is concerned, drops to 150/100 mm. Hg or less were considered significant by Fishberg[28] and Contratto and Rogers,[22] while Bryant and Blecha[20] considered a fall to 155/95 mm. Hg as significant. Smithwick, in sympathectomized patients, regarded the decrease in the diastolic pressure of 20 mm. Hg or to below 90 mm. Hg as significant.[29]

Of 874 patients on either the rice diet or the low-sodium diet, 213 (24 per cent) had a reduction of blood pressure to 155/100 mm. Hg or lower. If we analyze the hospitalized patients, we find that 25 of 112 patients (22 per cent) had reductions in blood pressure to 155/100 mm. Hg or below, while 188 of 752 ambulatory patients (25 per cent) had such a reduction. Adequate control periods before institution of the rice diet or the low-sodium diet were carried out in 212 patients. Of these, 46 (21 per cent) had blood pressure reductions to 155/100 mm. Hg or lower. If 150/100 mm. Hg is used as indicating a significant response, one finds that 166 of 681 patients (25 per cent) had such a fall. If one uses 145/95 mm. Hg as the standard of significant response, 133 of 550 patients (24 per cent) had such a fall in blood pressure. From these results there seems to be no statistical difference in taking 155/100 mm. Hg as the significant response as compared with 145/95 mm. Hg.

If one compares the results of dietotherapy with those following dorsolumbar sympathectomy, it is found that of 119 patients followed by Fishberg[28] before and after the operation, 22 (18.4 per cent) had a fall in blood pressure to 150/100 mm. Hg or below postoperatively. Of 439 unselected patients reported by Smithwick[29] and followed 1 to 5 years, 22 per cent fell into his classification of category 1, which means that the diastolic blood pressure was lowered 20 mm. Hg or more to below 90 mm. Hg by sympathectomy. One cannot make an absolute comparison here because of the difference in standards and because of the longer time that Smithwick had followed his patients.

It must be noted that the sympathectomized patients followed by Fishberg had an average preoperative blood pressure level of 218/135 mm. Hg. The 500 patients studied by Kempner[7] had an average pretreatment blood pressure of 198/116 mm. Hg and the 22 patients of Schroeder an average of 199/123 mm. Hg at the end of the control period.

Can a fall of blood pressure on the rice diet or a low-sodium diet be attributed to spontaneous remission? According to Perera,[30] who studied 250 patients with hypertensive vascular disease for an average period of 12 years without treatment, there was considerable variation in the individual case, but the general tendency in blood pressure was to increase but slowly throughout the years of observation, e. g., at the time of diagnosis the average blood pressure was 182/108 mm. Hg; at the time of last observation (excluding critically ill or terminal cases) the average blood pressure was 202/116 mm. Hg. However, Perera[31] stated that "it is less well recognized that normal blood pressure values may be obtained in as many as 15 per cent of patients with uncomplicated essential hypertension, even after decades of documented disease, following a period of prolonged rest or relaxation."

Between 1941 and 1944, Bechgaard,[32] in Copenhagen, was able to repeat the blood pressure on 709 living patients originally examined from 1932 to 1938. In the original examination hypertension was diagnosed in persons who showed a blood pressure of 180 mm. Hg systolic or 160/100 mm. Hg or higher. Among these 709 patients the second examination revealed a systolic blood pressure below 144 mm. Hg in 54 patients (7.6 per cent) and a diastolic pressure between 90 and 99 mm. Hg in 17 of these 54 patients. Therefore, 17 of the 709 patients (2.4 per cent) had blood pressure values of 144/99 mm. Hg or below which could be attributed to a spontaneous remission.

Comparison of the natural remission in 2.4 per cent of the patients with a reduction of the diastolic level to 100 mm. Hg or below with 24 per cent of the patients on the rice or low-sodium diet and 18.4 per cent of the patients after sympathectomy would seem to indicate that reduction of blood pressure with dietotherapy is due to more than spontaneous remission.

Dietotherapy would seem to have no significant effect on the blood pressure of patients with malignant hypertension. Four patients of Viersma,[17] 3 patients of Schroeder and associates,[24] and 3 of 4 patients of Megibow and associates[33] had no improvement by dietotherapy. The 1 patient of Megibow who was classified as having a good response was treated by accelerated sodium depletion by means of a low-sodium diet and mercurial injection. The blood pressure fell from 242/132 mm. Hg to 190/92 mm. Hg. The diagnosis of vascular retinopathy, the presence of which is one of the criteria for the diagnosis of malignant hypertension, may improve without a coincident decrease of blood pressure. Kempner reported a disappearance of very severe retinopathy in the presence of a constant high level or only insignificant reduction in blood pressure.[7]

MECHANISM OF ACTION

It is generally agreed that any relation that may exist between sodium and arterial hypertension is a complex one.[34] The possibility that there may be a

disturbance of sodium balance in hypertension was brought out by the studies of Perera and Blood.[35] Hypertensive patients placed on 24 hours of rigid salt restriction did not lose weight or water, while normal individuals did. Both groups lost the same amount of salt, but in 2 pairs of subjects the clearance of sodium was reduced in the hypertensive patient. The question has been raised as to whether or not the adrenals influence the kidney to retain salt. Adrenal dysfunction is related both to sodium balance and hypertension. Disease of the adrenals may be associated with hyponatremia (Addison's disease) or hypernatremia (adrenal cortical hyperfunction). Bilateral adrenalectomy will prevent the development of experimental hypertension and lower the blood pressure in established hypertension unless substitution therapy is used.[36] Hypertension is associated with tumors or hyperplasia of the adrenal cortex. The administration of desoxycorticosterone and salt will elevate the blood pressure in animals and humans.[36,37]

Stead and co-workers[38] studied the mechanism of action of the low-sodium diet by means of the relation of the fall of the blood pressure in response to an injection of tetraethylammonium chloride while the patient was on a low salt and on a full salt regimen. The idea was to evaluate the relative roles of neurogenic and humoral tone in the maintenance of blood pressure, the neurogenic element being eliminated in response to the injection of tetraethylammonium chloride. Five patients while on the low-sodium diet showed a significant lowering of the tetraethylammonium chloride floor, which is the blood pressure fall during the maximum effect of the drug. This was interpreted as indicating that the important change during sodium deprivation may be lessening of the humoral contribution to the maintenance of an increased peripheral resistance.

Viersma[17] indicated that the decrease in blood pressure during the administration of a low-sodium diet may be due to a decrease in the cardiac output, but this finding was not substantiated by others.[35,38]

The efficacy of the rice diet has been variously attributed to the low salt content, to the caloric restriction, to the low protein, or even to some unknown characteristic found in the rice. Kempner[39] himself suggested that the value of the diet lies in the compensation of renal metabolic dysfunction with a diet that decreases the metabolic activities of the kidney.

TOXIC EFFECTS

There are certain dangers inherent in salt depletion.[40] Some of the lesser ones are similar to those found in heat cramps and include vertigo, headache, apathy, anorexia, nausea, and twitching of the muscles. There may also be abdominal cramps.

Of more serious import is the danger of azotemia which seems to be less serious a problem in patients with normal renal function than in those with renal insufficiency. Schroeder[41] has pointed out that a low-salt syndrome might occur in patients who have renal insufficiency and are being deprived of salt as part of the treatment for hypertension. The syndrome is characterized by azotemia and hyponatremia. The treatment consists of intravenous administration of hypertonic saline solution. If undertreated, death may ensue.

Chasis[25] and associates have found that the administration of the rice diet may lead to a decrease of the filtration rate, renal blood flow, and maximal tubular excretory capacity.

The claim by Kempner that his patients are in nitrogen balance on an intake of 20 Gm. of protein daily has been questioned by Schwartz and Merlis.[42] The latter authors found on Kjeldahl analysis of the rice diet that the daily intake of nitrogen was 2.63 Gm. (representing an intake of 16.43 Gm. of protein) rather than the 3.28 Gm. (20 Gm. of protein) calculated from tables of food value. Further, the 6 normal patients and 1 hypertensive patient studied by Schwartz and Merlis[42] all showed a negative nitrogen balance after 8 days on the Kempner regimen with an average loss of 3.28 Gm. of nitrogen daily. The hypertensive patient, however, had a nitrogen loss which was less than the normal subjects after 90 days on the diet, although the blood pressure dropped significantly and symptoms were improved.

Peschel and Peschel[43] studied 11 patients who were on the rice diet for an average of 89 days. They showed that the nitrogen intake and nitrogen output were close to equilibrium in all 12 test periods. Five balances were slightly negative, 7 slightly positive. The average of the 5 negative balances was −0.39 Gm. daily. The average of the 7 positive balances as +0.70 Gm. daily. The average of the results of all the 12 tests was a positive balance of + 0.25 Gm. daily.

Watkin[44] did balance studies for 32 one-week periods on 13 hospitalized hypertensive patients maintained on a diet of rice, fruit, and sugar. Markedly negative nitrogen balances, and weight loss characterized the first 2 weeks of the diet. The output, largely urinary, exceeded intake by 3 to 8 Gm. daily. Of 30 periods studied after the first 2 diet weeks, 17 showed a mean negative nitrogen balance of −0.72 Gm. and 13 a mean positive balance of + 0.61 Gm. The data suggested to Watkin that negative balances occurring after the first 2 diet weeks are of inconsequential proportion and that most patients on the rice diet will eventually reach essential equilibrium.

SUMMARY

1. The blood pressure of the patient with hypertension can be lowered by different dietary methods. These include caloric reduction (controlled or unplanned semistarvation levels), the rice diet of Kempner, and the low-sodium diet. Weight reduction is responsible in part for the lowering of the blood pressure on the diets restricted in calories. The low-sodium content of the rice diet is the "hypotensive" factor since patients on this diet with a normal sodium intake do not have a fall in blood pressure. The low protein content (20 Gm.) of the rice diet is not essential to the lowering effects on the blood pressure, for similar falls in blood pressure have been recorded with a normal protein (70 Gm.) but a low-sodium content.

2. Reductions of blood pressure to 155/100 mm. Hg from higher levels were recorded in 24 per cent of 874 patients on either the rice or low-sodium diet. Of these, 212 adequately controlled patients showed a similar reduction in blood pressure in 21 per cent of the instances. To assess the significance of such

reductions in blood pressure, one must compare these figures to 18.4 per cent of the patients who had a fall in blood pressure to 150/100 mm. Hg or lower after sympathectomy, even though preoperative blood pressures were in approximately the same range as those treated by the rice or low-sodium diets.

Further, spontaneous remissions of the blood pressure during the natural course of hypertension to levels of 144/99 mm. Hg or below were found by Bechgaard to occur in 2.4 per cent of 709 patients and to normal pressures in 15 per cent of the patients with uncomplicated essential hypertension by Perera.

3. The mechanism of action of the rice and low-sodium diet has been attributed to the effect of the sodium ion on hypertension as mediated through the adrenals, to an effect of the sodium deprivation on lessening the humoral contribution to maintenance of an increased peripheral resistance, or to the decreased metabolic activities of the kidneys while on the rice diet.

4. Toxic effects of the rice and low-sodium diets vary from such minor effects as muscular pains to collapse associated with a "low-salt syndrome" and characterized by azotemia and hyponatremia. Nitrogen balance, though negative during the first 2 weeks on the rice diet, reaches essential equilibrium after this.

ADDENDUM

Since this review was written, a report by Griep and associates (Griep, A. H., Barry, G. R., Hall, W. C., and Hoobler, S. W.: The Prognosis in Arterial Hypertension: Report on 117 Patients Under 53 Years of Age Followed 8 to 10 Years, Am. J. M. Sc. **221**:239, 1951) was made on 117 patients, all of whom had blood pressures exceeding 160/110 mm. Hg on 2 or more occasions. All were under the age of 53 years at the start of the study. Of these 117 patients, 63 (53.8 per cent) were dead in 8 to 10 years. Of 44 survivors, only 2 (4.5 per cent) had a fall in blood pressure to normal levels.

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